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CASE REPORT

Albumin dialysis with MARS for the treatment of anabolic steroid-induced cholestasis

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ABSTRACT

Background and aims. Steroid-related hepatotoxicity has become one of the most relevant causes of drug induced liver cholestasis. Some patients do not improve after standard medical treatment (SMT) and may therefore require other approaches, like extracorporeal liver support. **Material and methods.** We report four cases of patients with pruritus, abnormal liver function tests and biopsy-proven anabolic steroid-induced cholestasis who were unresponsive to SMT. They underwent treatment with albumin dialysis (Molecular Adsorbent Recirculating System -MARS®-). A minimum of two MARS sessions were performed. **Results.** After MARS® procedure, patients' symptoms improved, as well as liver function tests, thus avoiding liver transplantation. **Conclusion.** Albumin dialysis appears as a valuable therapeutic option for the management of anabolic steroid-induced cholestasis in patients that are unresponsive to SMT.

Key words. Drug-induced liver disease. Cholestasis. Liver failure. Extracorporeal liver support. Pruritus

INTRODUCTION

The use of nutritional supplements and anabolic steroids is becoming increasingly widespread among the general population.[1-3] Steroids, particularly those containing a 17-alpha alkyl group, have been associated with the development of jaundice due to either cholestatic or hepatotoxic mechanisms.[4] Treatment of drug-induced cholestasis includes early drug withdrawal and medical support, which in most cases leads to a complete resolution of cholestasis. However, some patients do not improve after standard medical treatment (SMT) and may therefore require other therapeutic approaches, such as liver transplantation or extracorporeal liver support systems, particularly albumin dialysis with MARS® (Molecular Adsorbent Recirculating System).[5]

This is a case series of four patients with anabolic steroid-induced cholestasis who were unresponsive to SMT and underwent successful treatment with MARS®.

CASE REPORT

Presentation

We report a case series of 4 young adult male patients (mean age: 24.5 years, SD: 3.8) who presented with severe cholestasis after ingestion of Epithiostanol. Chief complaints were jaundice and pruritus. Asthenia was also present in two patients. Physical examination revealed skin and mucosal jaundice without hepatomegaly (except in patient 1). There were no signs of hepatic encephalopathy. Symptoms developed after a median of 4 weeks after the first dose of epithiostanol. Posology and duration of epithiostanol intake are shown in detail in table 1, as well as specific dates and timing.

Patients did not report use of alcohol, tobacco, illegal drugs, herbal remedies or over-the-counter drugs. There was no prior history of nutritional supplement use except for patient 1, who was taking a combination of multivita-

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Table 1. Demographic, clinical and laboratory parameters of patients with steroid-induced cholestasis.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	29	20	23	26
Gender	M	M	M	M
Weight (kg)	84	73	75	78
Comorbidities	Gilbert's disease	Thalassemia minor	None	None
Drug consumption (days)	21	33	58	30
Dose (mg)	54	162	60	30
Administration route	Oral	Oral	Oral	Oral
Time to onset (days)	30	33	31	30
Jaundice	Yes	Yes	Yes	Yes
Pruritus	Yes	Yes	Yes	Yes
Asthenia	No	Yes	No	Yes
Hepatomegaly	Yes	No	No	No
Hospitalization stay (days)	57	52	50	52
Levels at hepatotoxicity onset				
Alanine aminotransferase, U/L	169	344	109	300
Alkaline phosphatase, U/L	118	190	240	347
Total bilirubin, mg/dL	7.5	13	25	12.7
Creatinine, mg/dL	2.2	1.4	0.8	1.4
Peak values				
Alanine aminotransferase, U/L	155	63	109	300
Alkaline phosphatase, U/L	248	292	248	347
Total bilirubin, mg/dL	62	56.5	50.3	40.6
Creatinine mg/dL	2	2.3	0.8	1.4
Liver histology				
Cholestasis	++	++	++	++
Fibrosis	-	-	-	-
Inflammation	++	+	++	-
Iron deposition	-	-	-	-
Necrosis	+	+	-	-
RUCAM scale	7	8	7	7

min and protein supplements (the patient acknowledged the daily use of protein supplements without steroids up until a month before symptoms started).

At the diagnosis of hepatotoxicity, all patients presented with hyperbilirubinemia and elevation of alkaline phosphatase (ALP) as well as alanine aminotransferase (ALT), but only modest elevation on aspartate aminotransferase (AST). During hospitalization, bilirubin yielded an average peak value of 62 mg/dL, 4 weeks after the onset of symptoms (Figure 1).

Renal dysfunction was detected in 3 out of 4 patients. Serum creatinine values ranged from 1.5 to 2.2 mg/dL without proteinuria. Renal biopsy was performed in one of them (case 2) and it was reported as acute tubular necrosis with tubular deposits of biliary pigment

Blood cholesterol levels dropped to values of less than 10 mg/dL in 50% of patients.

Diagnostic workup

In all patients, alcohol history was insignificant and evaluation for viral hepatitis (including HAV, HBV, HCV, HEV, HIV and herpes viruses), autoimmune, genetic and metabolic liver diseases was negative. No patient had a prior medical or family history of liver disease or occupational exposure to potential hepatotoxic substances.

Both abdominal ultrasonography and magnetic resonance imaging (MRI) were normal. Finally, liver biopsy was performed in all patients. The most prominent finding was the accumulation of biliary pigment inside hepatocytes together with necrosis and a small number of neutrophil and eosinophil aggregates mostly in central areas, all of which suggested a toxic cause. There were varying grades of bile stasis with or without associated inflammatory damage.

The absence of other causes of liver disease, the temporal relationship between onset of symptoms and the use of the drug, and the normalization after its withdrawal were all highly suggestive of drug-induced liver injury. According to the RUCAM classification (Roussel Uclaf Causality Assessment Method)[6] the diagnosis of anabolic steroid-induced intrahepatic cholestasis was probable (RUCAM score between 7 and 8 points).

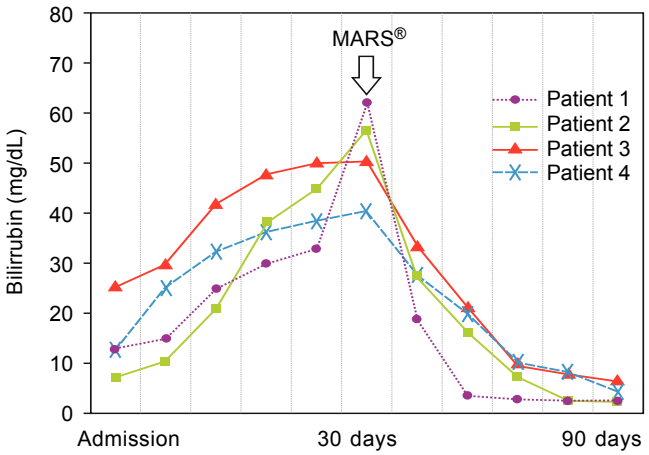

Figure 1. *Bilirrubin levels before and after MARS® therapy.*

Therapeutic intervention

After one month of hospital stay with standard medical treatment no improvement in clinical or laboratory parameters was noted. The medical team agreed that the patients had to be evaluated for liver transplantation and started extracorporeal albumin dialysis with MARS®. Clinical course and evolution of laboratory values are shown in table 2. The MARS® procedure was performed in the Intensive Care Unit (ICU) at a single-center (Hospital Universitari i Politècnic La Fe, Valencia, Spain) by the same operator. On admission into the ICU, patients had high-flux double-lumen catheters placed in the femoral vein and were then subjected to 7-hour sessions of MARS® per day. A minimum of two MARS sessions were performed, in two or three consecutive days of therapy. All patients were treated with the development of no significant complications (mild anemia in patients 2 and 3).

Follow-up and outcomes: After MARS® therapy, pruritus disappeared, serum ALP and bilirubin levels lowered, and renal function improved (Table 2). Patients were discharged from hospital and follow-up visits revealed almost normal laboratory tests and lack of symptoms. Laboratory results checked 4 months later showed normalization of liver function tests and creatinine.

DISCUSSION AND CONCLUSIONS

This case series illustrates severe cholestatic liver injury associated with the ingestion of Epithiostanol. The main lesson from this case series is that MARS therapy is a useful therapeutic option in this scenario.

Recently, the number of cases of anabolic steroid-induced liver toxicity has increased considerably, due to a rise in the sales of nutritional supplements containing steroid-based prohormones.[4,5] Most cases of anabolic steroid-induced cholestasis are not caused by direct hepatocellular damage but rather by an impaired biliary secretion. The mechanisms underlying this impairment are not fully understood, but it has been postulated that oxidative stress may produce damage to bile ducts by means of mitochondrial and lysosomal degeneration. Several anabolic steroids are available, but it is those containing the 17-alpha alkyl group that exhibit the greatest liver toxicity due to their slower absorption and metabolism rates. Epithiostanol is a synthetic testosterone-derived steroid, with enhanced anabolic properties and reduced androgenic effects.[7,8] It is considered a pro-hormone which suffers hepatic conversion into desoxymethyltestosterone. This substance has potentially harmful side effects that depend upon individual factors as well as duration of use, and that generally show up 1-5 months after initiating consumption.[1]

There is no specific therapy against drug-induced liver injury, and treatment is mainly supportive. After discontinuation of the suspected drug, close monitoring of hepatic enzyme levels is necessary. Some reports have proposed the use of N-acetylcysteine in the early phases of acute liver failure.[9] Cholestyramine and Ursodeoxycholic acid may be useful for alleviation of pruritus. Other drugs aimed to treat pruritus, like resins, rifampicin, or naltrexone, were not used in our patients. Elevation of serum bilirubin in steroid-induced liver toxicity may result in acute renal failure, a complication that generally resolves once cholestasis has been corrected.[2,4]

Since no specific antidote is available for the majority of hepatotoxic agents, interest in extracorporeal liver support systems is growing. Of these, the molecular adsorbent recirculating system (MARS®) is one of the most extensively studied. This system uses standard hemodialysis or hemofiltration equipment with the addition of an intermediate circuit containing 20% human albumin combined with a high-flux dialysis membrane. The closed-circuit albumin is passed through a conventional dialysis membrane, and then through an activated carbon absorber and anion exchanger that cleans it of albumin bound toxins and other water-soluble substances (so that regenerated albumin could be re-entered again in the system). In general terms, extracorporeal liver-support systems are able to remove both endogenous (ammonium, urea, bilirubin, biliary salts, amino acids, cytokines and vasoactive agents) and exogenous (drug metabolites and toxins) substances, which is why they may be useful for favoring liver recovery after drug-induced toxicity.

Several case reports published have shown the utility of MARS® therapy in drug-related liver toxicity,[10-15] but only a few assess its use in the case of anabolic steroid-induced liver toxicity.[16,17] Anand, *et al.*[18] published the case of a

Table 2. Analytical parameters before and after MARS® therapy.

	Patient 1	Patient 2	Patient 3	Patient 4
	Pre-MARS /Post-MARS*			
Total bilirrubin (mg/dL)	62/2.7	56.5/2.3	50.3/6.4	40.6/4.4
AST (IU/L)	66/47	65/23	70/92	153/73
ALT (IU/L)	155/86	63/22	109/118	300/128
ALP (IU/L)	248/134	292/142	248/116	347/127
GGT (IU/L)	28/23	36/41	109/116	30/27
Serum colesterol (mg/dL)	6/230	50/140	7/261	65/170
Creatinine (mg/dL)	2.0/1.1	2.3/0.9	0.83/0.54	1.44/1.28
MELD score	29/11	30/10	21/13	24/14

* Values shown in table the highest and lowest levels observed during hospitalization.

21-year-old male with Parabolan (trenbolone hexahydrobenzylcarbonate) overdose that developed acute cholestatic hepatitis which was unresponsive to medical treatment. Five MARS® cycles were performed; the procedure was well tolerated, leading to a sustained relief of pruritus and decrease in plasma bilirubin levels. In the 4 cases reported by our group, pruritus and liver function tests worsened despite standard medical care, and only after MARS therapy clinical and laboratory parameters improved immediately. MARS® therapy resulted in reduced bilirubin levels, relief of pruritus and icterus, and overall clinical improvement, with a consequent reduction in the duration of hospital stay. Moreover, our patients showed elevation in serum creatinine that resolved after MARS® therapy.

Regarding the outcomes of patients in hypothetical setting of absent MARS, our group published a case report of anabolic steroid-induced cholestasis who recovered after a month from drug withdrawal, so that extracorporeal liver support system was not indicated.[16] On the other hand, in the paper published by Heidemann, *et al.,*[19] reporting 6 cases or severe DILI, the majority of them recovered within 6 months, while in our case-series the four patients recovered in a more accelerated way due to MARS therapy. Our results reinforce the usefulness of MARS in this clinical scenario.

Research has also revealed potential benefits of MARS® therapy in several other liver-related conditions, such as refractory pruritus,[4,5,15] hepatic encephalopathy, portal hypertension, altered renal function and ascites. Pares, *et al.*[5] described the results of MARS in cohort of a variety of aetiologies, mainly rejection and primary biliary cirrhosis, but without cases of DILI. The strong point of our cohort is that we provide 4 well-characterized cases reports in the same clinical setting (severe cholestatic liver injury associated with the ingestion of Epithiostanol). Some studies have shown that this procedure could be used successfully as bridge therapy prior to liver transplantation in patients suffering from either acute or acute-on-chronic liver failure, regardless of whether the cause is drug-related or not. In spite of this, however, MARS therapy has not demonstrated a beneficial effect on patient survival.[14,20] Certain aspects such as the total number of MARS® sessions and the intervals at which they should be performed remain unclear.

In conclusion, albumin dialysis with the MARS® system appears as a valuable therapeutic option for the management of anabolic steroid-induced cholestasis in patients that are unresponsive to standard medical therapy.

ABBREVIATIONS

- **ALP:** alkaline phosphatase.
- **ALT:** alanine aminotransferase.
- **AST:** aspartate aminotransferase.
- **HAV:** hepatitis A virus.
- **HBV:** hepatitis B virus.
- **HCV:** hepatitis C virus.
- **HEV:** hepatitis E virus.
- **HIV:** human immunodeficiency virus.
- **ICU:** Intensive Care Unit.
- **MARS:** molecular adsorbent recirculating system.
- **MRI:** magnetic resonance imaging.
- **PT:** prothrombin time.
- **RUCAM:** Roussel Uclaf Causality Assessment Method.
- **SMT:** standard medical treatment.

CONFLICT OF INTEREST

All authors of the manuscript declare that they do not have anything to disclose regarding funding or conflict of interest.

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