CASE REPORT

Two case reports of corticosteroid administration—prolonged and pulsed therapy—in treatment of pruritus in cholestatic hepatitis A patients

Daad Daghman¹, Mohamad Saeed Rez², Amjad Soltany³,* and Almotaman Alsaleh⁴

¹Teacher of Gastroenterology, Department of Gastro-enterology Faculty of Medicine, Tishreen University, Lattakia, Syria, Teacher of Gastroenterology at Al Andalus University for Medical Science, Tartous, Syria, ²Department of Neurology, Al-Bassel Hospital, Tartus, Syria, ³Department of Plastic and Reconstructive Surgery, Al Mouwasat University Hospital, Damascus, Syrian Arab Republic, ⁴Department of Cardiology, Tishreen University Hospital, Lattakia, Syria

Abstract

Cholestasis following hepatitis A affects around 0.8% of hepatitis A patients. It is considered a distressing complication in spite of its good prognosis. Despite being subject to multiple studies, causes of cholestasis are still controversial. Many treatments (discussed later) have shown some improvements of the accompanied pruritus. In the following article, we present two cholestatic hepatitis A patients who suffered from severe pruritus. Prednisolone was administered via two different methods: prolonged and pulsed. Both showed great improvement of the pruritus in a short time frame. To the best of our knowledge, our management using pulsed corticosteroid therapy in treatment of pruritus in cholestatic hepatitis A is considered the first experimental management in medical literature. The importance of this experimental case lies in reducing the doses and the duration of steroid intake, thus reducing steroid side effects as far as possible.

INTRODUCTION

Hepatitis A is considered a self-limiting infectious disease with neither specific treatment nor recommended diet. Its rare complications include recurrence, acute liver failure and cholestasis. Cholestatic hepatitis is accompanied by elevated liver enzymes and increases in blood bilirubin levels, in addition to pruritus [1]. As this pruritus may be a gravely disabling symptom, numerous evidence-based therapeutic strategies (discussed later) are recommended.
Two case reports of corticosteroid administration-prolonged

| Table 1: |
|---------|
| Bilirubin | Alanine Aminotransferase (ALT) | Aspartate Aminotransferase (AST) | Antibodies against hepatitis C virus (Anti HCV) | Hepatitis B surface antigen (HBsAg) |
| Normal Range: 0-1 mg/dl | Normal Range: 5-45 U/l | Normal Range: 5-40 U/l | | |
| 10.9 mg/dl | 199 U/l | 270 U/l | Negative | Negative |
| anti-smooth muscle antibody (ASMA) | Anti-mitochondrial antibodies (AMA) | Antinuclear Antibodies (ANA) | HAV IgM antibody(anti-HAV IgM) | Ceruloplasmin |
| Negative | Negative | Negative | Positive: more than 1.0 | Normal Range: 20-35 mg/dl. |
| 25 mg/dl |

| Table 2: |
|---------|
| Bilirubin | Direct Bilirubin | Alanine aminotransferase (ALT) | Aspartate aminotransferase (AST) |
| Normal range: 0-0.25 mg/dl | Normal Range: 9-39 U/l |
| 22.5 mg/dL | 20.94 mg/dL | 32 U/l | 45 U/l |
| Gamma-glutamyl transferase (GGT) | Prothrombin time | International normalized ratio (INR) | Alkaline phosphatase (ALP) |
| Normal Range: 9-39 U/l | 58% | 1.34 | Normal range: 64-306 U/l |
| 22 U/l | 3.9 mg/dl. |

| Table 3: |
|---------|
| Bilirubin | Direct bilirubin | Alt | AST | PT |
| 15.9 mg/dl | 14.3 mg/dl | 30 U/l | 61 U/l | 100% |

| Table 4: |
|---------|
| Bilirubin | Direct Bilirubin | PT | INR |
| 7.8 mg/dl | 6.9 mg/dl | 100% | 1 |

Figure 1: Blood alkaline phosphatase (ALP) levels in patient 1.

Following 4 weeks of treatment with prednisolone, total bilirubin level reached 2.27 mg/dl. See Fig. 1.

Case 2

A 30-year-old female presented with nausea, vomiting and anorexia. Physical examination revealed tenderness in the right hypochondrium. No other significant clinical findings in her physical examination were found.

Admission work-up is shown in Table 5.

| Table 5: |
|---------|
| Bilirubin | Direct Bilirubin | ALT | AST | GGt | ALP Normal Range: 64-306 U/l |
| 1.4 mg/dl | 1 mg/dl | 1440 U/l | 1500 U/l | 168 U/l | 110 U/l |
| HAV IgM | HBsAg | Anti HCV | Ceruloplasmin | ANA | ASMA |
| Positive: more than 1.0 | 2.94 (positive) | Negative | Negative | 24 mg/dl | Negative |
DISCUSSION

Hepatitis A is a self-limiting disease where recovery usually starts at around 7–14 days following the onset of symptoms. Hepatitis A can become cholestatic in about 0.8% of patients [2]. Cholestasis is a result of impaired metabolism and flow of bile in the liver [3]. Many different causes of this issue have been proposed. These causes include genotypes and sub-types of hepatitis A viruses. It was discovered that the sub-types 1a and 1b were responsible for the long-term nature of the disease because of the difficulty of producing antibodies against these two sub-types [1]. The exchange of nucleotides in the mid-section of the untranslated sector 5 may also intervene with the severity of the damage [1]. In addition, cytokines and other inflammatory promoters like TNF-α and IL1 play a role in causing cholestasis [2, 4].

The virus may also cause spotty necrosis in the perportal space that interrupts the continuity of bile flow to portal ducts due to secondary immune reaction [5]. Cholestatic hepatitis also causes interlobular bilirubin accumulation especially in zone 3 as well as necrosis in the infected hepatocyte caused by cluster differentiation 8 (CD8) positive T cells [6], in addition to endotoxin released by the liver [2].

The patient was diagnosed with hepatitis A (on the basis of elevated HAV IgM antibodies and negative serology for hepatitis B, C). Five days later, jaundice and pruritus became apparent. The anorexia persisted for a week accompanied with severe nausea and pruritus.

Follow-up laboratory values are shown in Table 6. Ten days later, the severe pruritus persisted and laboratory values were repeated again (Table 7).

On the same day, prednisolone was administered as a pulsed therapy for 4 days starting with 30 mg for the first day, then 20 mg, 10 mg and 10 mg once daily, respectively, for each of the following days. The pruritus gradually improved on the second day and disappeared completely at the end of the fourth day with values shown in Table 8. Five weeks later, the follow-up laboratory values are shown in Table 9. See Fig. 2.

| Table 6: | Bilirubin | Direct bilirubin | ALT | AST |
|----------|-----------|-----------------|-----|-----|
| 12.9 mg/dl | 10 mg/dl | 1705 U/l | 545 U/l |
| ALP 180 U/l | PT | INR | 1.46 |
| 59% |

| Table 7: | Bilirubin | Direct bilirubin | ALT | AST | Alkaline phosphatase (ALP) | GGT |
|----------|-----------|-----------------|-----|-----|----------------------------|-----|
| 10.38 mg/dl | 8.9 mg/dl | 380 U/l | 230 U/l | 100 U/l |

| Table 8: | Bilirubin | Direct bilirubin | ALT | AST |
|----------|-----------|-----------------|-----|-----|
| 3.3 mg/dl | 2.5 mg/dl | 60 U/l | 55 U/l |
| GGT 101 U/l | ALP | 125 U/l |

| Table 9: | Bilirubin | Direct bilirubin | ALT | AST | GGT | ALP |
|----------|-----------|-----------------|-----|-----|-----|-----|
| 0.75 mg/dl | 0.5 mg/dl | 24 U/l | 35 U/l | 16 U/l | 100 U/l |

The compounds that are thought to have a role in triggering pruritus in patients with cholestasis following hepatitis A are shown in Table 10.

As a result of all these studies, many treatments were found for pruritus which is considered the most distressing and persistent symptom in patients with cholestatic complications. However, no final treatment is recommended since drugs react differently in different patients.

One of these treatments is ursodeoxycholic acid (UCDA) that lowers levels of transient bile salts and levels of bilateral sulfide steroids hence reducing the pruritus [7]. Additionally, there is a group of drugs that work on promoting metabolism of liver by stimulating cytochrome P 450 enzymes, such as rifampicin and phenobarbital [3].

Opioid inhibitors such as naltrexone could be used in addition to anesthetic drugs like lidocaine, antihistamines and resins that prevent the reabsorption of bile salts from the intestines such as cholestyramine. Serotonin reuptake inhibitors such as sertraline, phototherapy and molecular adsorbent recirculating system (MARS) are also administered for this purpose [5]. Corticosteroids have shown considerable efficacy in achieving symptom resolution in previous studies [8–9].

As for our previous two patients, they were given prednisolone in two different ways; the male was given steroids for 10 weeks with a starting dose of 40 mg tapered by 5 mg weekly (conventional or prolonged therapy). The female was given 30 mg for the first day, then 20 mg, 10 mg and 10 mg, respectively, for each of the following 3 days (pulsed therapy).

Both patients showed marked improvement and the distressing pruritus decreased after a few days of therapy (Table 11).

Figure 2: Blood alkaline phosphatase (ALP) levels in patient 2.
Two case reports of corticosteroid administration—prolonged

Table 10:

| Bile salts                        |  
|-----------------------------------|
| Bile salts play a major role in pruritus, but several studies observed that there is no connection between the severity of the pruritus and the concentration of different bile salts in plasma, although it has been confirmed that bile salts have an indirect effect that needs further studies [7]. |

| Lysophosphatidic acid (LPA)       |  
|-----------------------------------|
| Lysophosphatidic acid (LPA) also plays a role in pruritus since its concentration increases in patients with cholestasis, this was explained as a result of over-expressing autotaxin gene, leading to over-converting lysophosphatidyl choline (LPC) to lysophosphatidic acid [8]. |

| Opiates                           |  
|-----------------------------------|
| Opiates were also found to play a role in pruritus by activating μ receptors which may cause pruritus.[3–8]. |

| Progesterone sulfates             |  
|-----------------------------------|
| Progesterone sulfates and other products of cholestasis could alter the neurological reaction on both spinal cord and brain levels [3–8]. |

| Other compounds                   |  
|-----------------------------------|
| Serotonin, gastrin-releasing peptide (endovanilloid) and their receptors. |
| - Transient receptor potential cation channel sub-family V member 1 (Tprv-1), capsicin-r as well as cannabis, gamma-aminobutyric acid (GABA) and histamine inhibitors have been mentioned [3–8]. |

Table 11:

| Date       | Bilirubin | Date       | Bilirubin |
|------------|-----------|------------|-----------|
| 4/3/2015   | 10.9 mg/dl| 4/4/2016   | 1.4 mg/dl |
| 17/3/2015  | 16.3 mg/dl| 3/5/2016   | 10.4 mg/dl|
| 25/3/2015  | 19.5 mg/dl| 18/5/2016  | 12.9 mg/dl|
| 28/3/2015  | 22.5 mg/dl| 19/5/2016  | Corticosteroids Therapy Started |
| 30/3/2015  | Corticosteroids Therapy Started | 9/4/2015 | 11.8 mg/dl |
| 15/4/2015  | 7.8 mg/dl  | 11/7/2016  | 0.8 mg/dl  |
| 3/5/2015   | 2.27 mg/dl | 24/5/2016  | 3.3 mg/dl  |

FUNDING

None to declare.

THE GUARANTOR

Amjad Soltany, MD.

CONSENT

Written consent received.

REFERENCES

1. Coppola N, Genovese D, Pisaturo M, Taffon S, Argentini C, Pasquale G, Sagnelli C, Piccinino F, Rapicetta M, Sagnelli E. Acute hepatitis with severe cholestasis and prolonged clinical course due to hepatitis a virus 1a and 1b coinfection. Clin Infect Dis 2007;44:e73–e77. https://doi.org/10.1086/513430.
2. Trauner M, Fickert P, Stauber RE. Inflammation-induced cholestasis. J Gastroenterol Hepatol 1999;14:946–59.
3. Kremer AE, Beuers U, Oude-Elferink RPJ, Pusl T. Pathogenesis and treatment of pruritus in cholestasis. Drugs 2008;68:2163–82.
4. Yoon EL, Yim HJ, Kim SY, Kim JH, Lee J-H, Lee YS, Lee HJ, Jung SW, Lee SW, Choi JH. Clinical courses after administration of oral corticosteroids in patients with severely cholestatic acute hepatitis A; three cases. Korean J Hepatol 2010;16:329–33. doi: 10.3350/kjhep.2010.16.3.329.
5. Sciot R, Damme BV, Desmet V. Cholestatic features in hepatitis A. J Hepatol 1986;3:172–81.
6. Stapleton JT. Host immune response to hepatitis a virus. J Infect Dis 1995;171:S9–S14. https://doi.org/10.1093/infdis/171.Supplement_1.S9.
7. Imam MH, Gossard AA, Sinakos E, Lindor KD. Pathogenesis and management of pruritus in cholestatic liver disease. J Gastroenterol Hepatol 2012;27:1150–8.
8. Garden JM. Pruritus in hepatic cholestasis. Pathogenesis and therapy. Arch Dermatol 1985;121:1415–20.
9. Pulluçu H. Use of steroids for prolonged cholestasis secondary to acute hepatitis A infection. J Microbiol Infect Dis 2014;4:162–4.