ADVANCES IN HEPATOLOGY

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Management of Pruritus in Patients with Cholestatic Liver Disease

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G&H How frequently does pruritus occur in patients with cholestatic liver disease? Is this symptom more commonly associated with certain types of cholestatic liver disease?

CL Some studies have reported pruritus in up to 70% of patients with cholestatic liver disease, although more recent studies have reported lower rates (20–30%). Pruritus is most common in patients with primary biliary cirrhosis, primary sclerosing cholangitis, and intrahepatic cholestasis of pregnancy, but pruritus is also fairly common in patients with chronic viral hepatitis, especially hepatitis C virus infection.

G&H How often is severe pruritus associated with cholestatic liver disease? What causes this symptom?

CL Data on the prevalence of severe pruritus are lacking, but I estimate that 5–10% of patients will have pruritus that is severe and refractory to available medical therapy. Similarly, more data are needed regarding the pathogenesis of pruritus. Currently, there are 2 main lines of thought: One hypothesis suggests that accumulation of bile salts in the plasma and tissues of patients with cholestatic disease leads to pruritus; the other theory suggests that endogenous opioids play a key role in the development of pruritus. However, investigators have not been able to demonstrate a strong, direct correlation between clinical reports of itching and the presence of either of these pruritogenic substances. In addition, patients do not always respond to therapy targeting either of these conditions.

Recently, however, a striking correlation was found between itching and the presence of lysophosphatidic acid (LPA), a potent neuronal activator. Furthermore, patients with pruritus have been shown to have increased levels of autotaxin, the enzyme responsible for the formation of LPA. These findings suggest that LPA and autotaxin play a role in the generation of pruritus. Hopefully, this finding will lead to the development of more effective therapies for pruritus, but more research is needed.

G&H Why is appropriate management of pruritus an important aspect of treatment for cholestatic liver disease?

CL Appropriate management of pruritus is very important. Pruritus can be very distressing for patients and can lead to a marked decrease in quality of life due to impaired sleep and depression; in some cases, pruritus may even result in suicidal ideation. On rare occasions, pruritus can be so debilitating that this symptom alone can justify a patient's listing for liver transplantation.

G&H Do standard therapies for cholestatic liver disease help to relieve pruritus?

CL In most cases, treatment of the underlying condition does not relieve pruritus. While all patients with primary biliary cirrhosis are given ursodeoxycholic acid (UDCA) to halt progression of their disease, UDCA

does not provide relief from pruritus in these patients. However, UDCA does provide relief of pruritus in patients with intrahepatic cholestasis of pregnancy. In general, therapy for cholestatic liver disease needs to be supplemented with pruritus-specific therapies in patients who experience this symptom.

G&H What medications can be used to manage pruritus in patients with cholestatic liver disease?

CL Practice guidelines on the management of pruritus are available from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Despite the lack of well-conducted, randomized, controlled studies, cholestyramine is still recommended as a first-line therapy for management of pruritus. Second-, third-, and fourth-line therapies include rifampicin, opiate antagonists (such as naloxone and naltrexone), and the serotonin reuptake inhibitor sertraline, respectively. For patients with intrahepatic cholestasis of pregnancy, treatment with UDCA improves both pruritus and liver function.

Unfortunately, there have been few rigorous studies to confirm the efficacy of these treatments, and available studies have included only a small number of patients. Nonetheless, some of these studies have shown benefit for various therapies. A controlled study of sertraline showed a 33% improvement in pruritus scores, and a small, placebo-controlled trial of naltrexone showed that total pruritus scores were decreased by 50% among treated patients, compared to a maximum decrease of 20% in the placebo group. My clinical experience has been that response rates below 50% are common for most of the drugs used to treat pruritus.

G&H What side effects are associated with these medications?

CL Cholestyramine is associated with gastrointestinal side effects—including nausea, bloating, and constipation—that often make this drug difficult for patients to tolerate. Furthermore, cholestyramine is a bile-acid resin, so it must be taken at least 4 hours before or after any other medications; this scheduling constraint can make this medication inconvenient for patients to take. To help minimize side effects with this drug, I start patients at a low dose and progressively increase the dose over subsequent days or weeks, as needed. Also, I warn patients in advance about the potential side effects of this drug, as I have found that patients are more likely to tolerate these symptoms when they know what to expect. Finally, I recommend that patients take cholestyramine at night so they can sleep through most of the side effects.

With rifampicin, patients face a 10–15% risk of acute hepatitis, so this drug is contraindicated in patients with advanced disease who have elevated bilirubin levels. With opioid antagonists, patients can experience withdrawal-like symptoms; however, starting these drugs at a very low dose and then progressively increasing the dose generally improves patients' tolerance to the medication. Finally, sertraline is usually well tolerated, but it can cause dry mouth, anxiety, drowsiness, and gastrointestinal side effects (including nausea and constipation).

G&H Is the molecular adsorbent recirculating system an effective treatment for pruritus associated with cholestatic liver disease?

CL The molecular adsorbent recirculating system (MARS) is an extracorporeal hemofiltration system that uses an albumin-enriched dialysate to remove albumin-bound substances. While data on this treatment option are limited, several small studies and case series have evaluated the use of MARS for treatment of pruritus associated with cholestatic liver disease. The largest such study evaluated 20 patients with severe refractory pruritus who were undergoing therapy with MARS; it found that MARS improved pruritus in 75% of patients. Given that the maximal response rate with available medical therapies is around 50%, this improvement represents a substantial response. In addition, even though pruritus partially returned 30 days after treatment, the severity of this symptom remained significantly lower than it had been at baseline.

Because this study was not placebo-controlled, the possibility of a placebo effect cannot be excluded. However, observed changes in autotaxin levels suggest that MARS has a real impact. In a study of 15 patients with severe pruritus who underwent treatment with MARS, improvement in pruritus correlated with a reduction in autotaxin levels, and subsequent recurrence of pruritus correlated with autotaxin levels returning to baseline. These findings are consistent with the hypothesis that LPA and autotaxin are involved in the pathogenesis of cholestatic pruritus, and they support the observed reduction in symptoms with MARS treatment. Further study of this new treatment modality is needed.

G&H Are there any other ways to manage pruritus associated with cholestatic liver disease?

CL Yes, several other treatment options can be considered, if necessary. Nasobiliary drainage is known to temporarily decrease the intensity of pruritus, and researchers have reported a concomitant drop in autotaxin activity with this treatment. In addition, anecdotal reports suggest that plasmapheresis can be effective in the treatment of

pruritus, but this benefit has not been confirmed in controlled studies. Finally, additional treatment modalities have been suggested, including vagal nerve stimulation and use of transdermal buprenorphine. Liver transplantation is rarely considered to manage pruritus associated with cholestatic liver disease.

G&H What further research is needed regarding management of pruritus in patients with cholestatic liver disease?

CL Given recent findings about the potential role of LPA in pruritus, an obvious area of interest is how to modulate LPA receptors and autotaxin activity to relieve pruritus. In addition, use of MARS to treat pruritus needs to be further evaluated in controlled studies, and the duration of MARS therapy needs to be defined; currently, we do not know how long or how often patients need to be treated with MARS to achieve relief of pruritus. Finally, significant progress has already been made in terms of developing instruments to assess pruritus, but this is an area that requires ongoing effort.

Suggested Reading

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