Off-Label Drug Uses

Ciprofloxacin: Spontaneous Bacterial Peritonitis (Prevention)

Joyce A. Generali, RPh, MS, FASHP (Editor),* and Dennis J. Cada, PharmD, FASHP, FASCP†

This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Spontaneous bacterial peritonitis (SBP), a bacterial infection of the ascitic fluid, is defined as an ascitic fluid polymorphonuclear (PMN) leukocyte count of 250 cells/mm³ or greater without evidence of an intra-abdominal, surgically treatable source of infection.¹ Although the exact mechanism by which ascitic fluid becomes infected in patients with cirrhosis has not been established, it is thought to occur via translocation of intestinal organisms from the lumen through the intestinal wall to the lymphatic system.² SBP is caused primarily by gram-negative enteric organisms, most commonly *Escherichia coli* and *Klebsiella pneumoniae*; pneumococci are also common in SBP.¹ Bacterial infection, including SBP, is a frequent complication in patients with advanced cirrhosis and gastrointestinal (GI) bleeding and has been associated with increased mortality. Risk factors for the development of SBP in cirrhotic patients include acute GI bleeding, a history of SBP, or low ascitic fluid protein concentrations (<1.5 g/dL) with or without impaired renal function or liver failure.¹

PATIENT POPULATION

Adults with liver cirrhosis and a history of SBP or low ascitic fluid protein concentrations (<1.5 g/dL).

DOSAGE AND DURATION

Long-term prophylaxis: 500 mg orally daily (preferred).³ Weekly dosing of 750 mg orally for long-term prophylaxis has been studied, but concerns regarding quinolone bacterial resistance limit use.^{1,4} American Association for the Study of Liver Diseases (AASLD) guidelines note that intermittent dosing (ie, 5 days/week, weekly) of antibiotics, although shown to be effective in SBP prevention, may be inferior to daily dosing due to development of bacterial resistance. Daily dosing regimens are preferred.¹

DISCUSSION

Guidelines

American Association for the Study of Liver Diseases

AASLD clinical practice guidelines on the management of adult patients with ascites due to cirrhosis recommend that SBP prophylaxis therapy include a 7-day regimen with intravenous ceftriaxone or oral norfloxacin in patients with cirrhosis and GI hemorrhage (class I recommendation; level A evidence). The guidelines suggest initiation with a parenteral antibiotic during an active bleeding episode, followed by an oral antibiotic once oral intake is resumed (total treatment duration of 7 days). For patients who have

*Editor-in-Chief, *Hospital Pharmacy*, and Clinical Professor, Emeritus, Department of Pharmacy Practice, University of Kansas, School of Pharmacy, Kansas City/Lawrence, Kansas, e-mail: jgeneral@ku.edu; †Founder and Contributing Editor, *The Formulary*, and Editor, *Off-Label Drug Facts*, e-mail: Dennis.Cada@wolterskluwer.com.

experienced a prior SBP episode, long-term secondary prophylaxis with daily norfloxacin or trimethoprim-sulfamethoxazole is recommended (class I recommendation; level A evidence). In patients with cirrhosis and ascites, long-term use of norfloxacin or trimethoprim-sulfamethoxazole may be used if patients have low ascitic fluid protein concentrations (<1.5 g/dL) in addition to impaired renal function (creatinine of ≥ 1.2 mg/dL, serum urea nitrogen [BUN] of ≥ 25 mg/dL, or serum sodium of ≤ 130 mEq/L) or liver failure (Child-Pugh score of ≥ 9 and bilirubin of ≥ 3 mg/dL) (class I recommendation; level A evidence). The guidelines note that intermittent dosing of antibiotics, although shown to be effective in SBP prevention, may be inferior to daily dosing due to development of bacterial resistance; daily dosing is preferred. Intermittent dosing regimens for SBP prophylaxis in patients with cirrhosis and ascites are mentioned in the discussion section of the guidelines but are not included in the final recommendations. The intermittent dosing regimens include 5 doses of double-strength trimethoprim-sulfamethoxazole (160 mg/800 mg) per week or a once-weekly oral dose of ciprofloxacin.¹

European Association for the Study of the Liver

EASL clinical practice guidelines on the management of ascites, SBP, and hepatorenal syndrome in cirrhosis state that in patients with GI bleeding and severe liver disease, ceftriaxone is considered the prophylactic agent of choice. In patients with GI bleeding and less severe liver disease, prophylaxis with oral norfloxacin or an alternative oral fluoroquinolone may be used to prevent the development of SBP (grade 1 recommendation; level A evidence). In patients with severe liver disease, low ascitic fluid protein concentration (<1.5 g/dL), and no prior SBP, daily norfloxacin should be considered for long-term primary prophylaxis (grade 1 recommendation; level A evidence). Use of fluoroquinolones for preventing SBP or improving survival has not been clearly established in patients with moderate liver disease, low ascitic fluid protein concentration, and no history of SBP. In patients who have experienced a prior SBP episode and are at high risk of recurrence, daily norfloxacin is also considered the secondary prophylactic treatment of choice (grade 1 recommendation; level A evidence). Alternative antibiotic recommendations supported by lower levels of evidence include oral ciprofloxacin once weekly or oral trimethoprim-sulfamethoxazole daily.²

Controlled Trials

In a double-blind, placebo-controlled, multicenter trial, 100 adult patients with cirrhosis and low ascitic total protein concentrations (<1.5 g/dL) without prior episodes of SBP were randomized to receive oral ciprofloxacin (500 mg) or placebo daily for 1 year. There were no significant differences between the 2 groups for clinical and laboratory features of liver disease at baseline. Diagnoses of SBP were confirmed by PMN counts greater than 250 cells/mm³, with or without positive cultures. Mean follow-up periods were 7.6 months and 7.8 months in the ciprofloxacin and placebo groups, respectively. Incidence of SBP, though lower in the ciprofloxacin group than in the placebo group (4% vs 14%), was not statistically different ($P = .07$). However, the probability of survival at 1 year was significantly higher in the ciprofloxacin group (86% vs 66%; $P < .04$). Absolute risk reduction was 17% (CI, 1% to 33%), relative risk reduction was 59% (CI, 0% to 83%), and the number needed to treat was 6 patients (CI, 3 to 76 patients). SBP, GI bleeding, and sepsis were the most frequent causes of death in the placebo group (3 each). Liver failure and GI bleeding were the most frequent causes of death in the ciprofloxacin group (2 each). The authors concluded that patients with cirrhosis and low ascitic total protein concentrations may be candidates for long-term prophylaxis.³

In a prospective, double-blind, placebo-controlled study, 60 adult patients with cirrhosis and low ascitic protein concentrations (≤ 1.5 g/dL) were randomized to receive once-weekly dosing with ciprofloxacin 750 mg orally ($n = 28$) or placebo ($n = 32$) for 6 months. Seven patients had experienced prior episodes of SBP (more than 3 months prior to enrollment), of which 1 occurred in the placebo group. Diagnoses of SBP were confirmed by PMN counts greater than 250 cells/mm³ and identification of organisms by microscopy or culture. Incidence of SBP was significantly lower in the ciprofloxacin group (3.6% vs 22%; $P < .05$), as was duration of hospitalization (9.3 vs 17.6 days; $P < .05$). Although 10 patients died during the study (4 in the ciprofloxacin group and 6 in the placebo group), no deaths were related to SBP. Bacteriological evaluation of fecal samples in 10 patients in the ciprofloxacin group showed no acquired resistance to ciprofloxacin after 6 months of therapy.⁴

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg,

Warnings/Precautions, Adverse Reactions, Drug Interactions).

Oral and injectable fluoroquinolones have a black box warning regarding an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients (usually those older than 60 years), in patients taking corticosteroids, and in patients with kidney, heart, or lung transplants. Fluoroquinolones may also exacerbate muscle weakness in myasthenia gravis and should be avoided in patients with a known history of myasthenia gravis.

Increasing resistance rates to antibiotics used in the treatment and prevention of SBP have been documented; local epidemiological patterns should be considered when selecting therapy.^{5,6} In a small study enrolling cirrhotic patients, intermittent ciprofloxacin therapy regimens (1,000 mg once-weekly dosing) were associated with lower eradication rates of gram-negative bacilli and higher rates of development and/or selection of quinolone-resistant bacterial strains.⁷ Due to concerns regarding bacterial resistance rates associated with weekly dosing regimens in SBP prophylaxis, AASLD guidelines recommend a daily dosing regimen over intermittent dosing.¹ Some expert panels also recommend that weekly regimens be avoided.⁸

THERAPY CONSIDERATIONS

Limited data from controlled trials support use of ciprofloxacin as an alternative to norfloxacin for primary long-term prophylaxis in cirrhotic patients with low protein ascites or as secondary long-term prophylaxis in patients who have experienced a prior SBP episode. Additional trials may be necessary to further define the role of ciprofloxacin in the prevention of SBP.

According to AASLD and EASL guidelines, ciprofloxacin is suggested as an alternative to norfloxacin; however, recommendations regarding the use of daily or weekly dosing vary. The AASLD prefers daily dosing, given the risk of increasing quinolone bacterial resistance rates with weekly dosing. Increasing

bacterial resistance rates to antibiotics used in the treatment and prevention of SBP have been documented; therefore, local epidemiological patterns should be considered, and use of antibiotic prophylaxis should be restricted to patients at high risk of SBP.

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