DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

Triple Therapy for Chronic Hepatitis C

Genotype 1 is the most difficult of the 6 hepatitis C genotypes to treat. Currently, the preferred approach is a combination treatment with pegylated interferon (PEG-IFN) plus ribavirin (RBV) in patients with an uncomplicated infection, but only half of patients reach sustained viral response (SVR) at 24 weeks; the rates are even lower in black patients: as low as 19%.

The protease inhibitors (PIs) telaprevir and boceprevir are new entries into the arena, approved for triple therapy: PI plus PEG-IFN (alfa 2a or alfa 2b) plus RBV. Telaprevir and boceprevir are reversible, selective, and orally bioavailable.

According to their review of 8 studies involving 4,144 treatment-naïve and treatment-experienced patients, researchers from the Massachusetts College of Pharmacy and Health Sciences in Worcester, Massachusetts, say both PIs increase the likelihood of early SVR. However, the researchers add that no direct, randomized trials have compared the 2 agents.

Triple therapy resulted in more patients reaching SVR at 24 and 48 weeks but also resulted in more drug-related adverse events (AEs); however, triple therapy did not lead to more patients discontinuing treatment. Because PEG-IFN plus RBV therapy produces some type of treatment-related AEs in nearly all patients, the researchers expected more discontinuations when telaprevir was added to the regimen. Fewer data were available on early response to therapy and discontinuations with boceprevir.

Because the 2 protease inhibitors have similar mechanisms of action, clinicians may consider them interchangeable. However, an indirect treatment comparison favored telaprevir for inducing 24-week SVR in treatment-naïve patients. Telaprevir triple therapy also caused additional rash, pruritus, and anemia. Boceprevir improved the odds ratio for both treatment-naïve and -experienced patients but with more treatment-related anemia and impaired sense of taste. The researchers say discussing the expected adverse drug reactions (ADRs) with patients is crucial, because each drug has a unique AE profile and different patient populations show highly variable rates of ADRs.

The 2 drugs also differ in food requirements and pill burden. For instance, patients on boceprevir take 4 capsules every 8 hours. By contrast, patients on telaprevir take 2 tablets every 8 hours but also have to take in at least 20 g of fat every 8 hours.

The reviewers were unable to find published literature that did not use 24- or 48-week SVR to demonstrate efficacy. So far there are no data on longer-term outcomes, such as the risk of hepatocellular carcinoma and hepatic-related mortality.

Source: Sitole M, Silva M, Spooner L, Comee MK, Malloy M. *Clin Ther.* 2013;35(2):190-197. doi: 10.1016/j.clinthera.2012.12.017.

The Arguments Against Sodium Polystyrene Sulfonate

Sodium polystyrene sulfonate (SPS) is widely used to treat hyperkalemia, but its efficacy is surprisingly at odds with the "very weak level of evidence," say researchers from the University of Toronto and Mount Sinai Hospital, both in Toronto, Canada. They note that, in early use, SPS was administered as a suspension in water until concerns about constipation and life-threatening intestinal impaction led to the common practice of administering it with sorbitol, an osmotic laxative. However, reports of fatalities related to colonic necrosis were "accumulating" and have continued to accumulate, although preparations of SPS containing 70% sorbitol, the postulated culprit, have been removed from the market and even though current versions of the product are low-sorbitol and no-sorbitol.

Despite the black-box warning and debate about whether the product is actually effective in reducing serum potassium levels, the drug continues to be widely prescribed for acute and chronic hyperkalemia. That may be placing patients at unnecessary risk, the researchers charge. They say that there have been no systematic attempts to identify and document cases of harm related to SPS use, so they decided to rectify the omission. The researchers did not plan a meta-analysis, since the published literature was made up of case reports. However, after applying their own exclusion criteria, they ended with 30 articles describing 58 cases of adverse events (AEs).

Notably, 91% of cases in this review had a history of acute kidney injury, chronic kidney disease, or end-stage renal disease. The researchers note that patients with renal disease have elevated renin levels, which predispose them to nonocclusive mesenteric ischemia. That risk may be heightened in the postoperative period due to such factors as concomitant hypotension, ileus-induced colonic distension, and reduced gut motility. Recent transplant patients are at particular risk because of immunosuppressive medications that impair the normal protective mechanisms of gastrointestinal (GI) cells. Those pathophysiologic processes, the researchers say, may be potentiated by the concomi-

tant use of sorbitol, which is believed to directly damage intestinal mucosa.

However, SPS crystals were commonly found aggregated within the injured areas of the GI tract histopathologic specimens. Although previous reports attributed the majority of GI AEs to 70% sorbitol-SPS preparations, the researchers in this study found only 1 report associated with that concentration (most reports did not give the concentration of sorbitol). They note, as well, that their review included cases in which patients given SPS without sorbitol also had GI AEs. And while some reports alluded to the crystals as the "footprint" of SPS, the researchers say their review suggests that SPS may be pathogenic. They cite other research that demonstrated that inoculating tissue with SPS leads to an acute inflammatory reaction within 24 hours. The pathogenesis of bowel injury related to SPS is "likely more complex than our current understanding," they conclude.

Source: Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. *Am J Med.* 2013;126(3):264.e9-264.e24. doi: 10.1016/j.amjmed.2012.08.016.

Low-Dose Vaporized Marijuana Relieves Neuropathic Pain

Neuropathic pain is a wild card of sorts, hard to diagnose and hard to treat—even the National Institutes of Health says current treatments are at best marginally effective. Studies of treatment with cannabis have had promising results, but they've typically used high doses (8% delta-9-tetrahydrocannabinol [THC]) or medium doses (4% THC). However, the higher doses come with negative cognitive effects.

Researchers from the VA Northern California Health Care System and the University of California, both in Sacramento; and from the University of California in San Diego, speculated that there might be a middle ground. They conducted a study to compare medium-dose (3.53% THC) with low-dose (1.29% THC) cannabis, aiming to find out whether the low dose would relieve pain while protecting against cognitive and psychotomimetic effects. In addition, the study examined vaporization as an alternative to smoking cannabis, which has drawbacks such as exposure to tar. In vaporization, the cannabis is heated to a temperature where active cannabinoid vapors form, but below the point of combustion where irritating respiratory toxins are released.

The participants were required to have previous exposure to cannabis to reduce the risk of adverse psychoactive effects in naïve individuals. They were also screened for depression to make sure they would be able to tolerate the psychoactive effects of cannabis.

Patients were scheduled for three 6-hour sessions, separated by at least 3 days to allow time for the THC metabolites to break down. They received low-dose or medium-dose cannabis or placebo at each visit in a crossover design; each patient received each treatment once. The researchers used visual analog scales to assess for pain relief and psychoactive effects. Neurocognitive assessments focused on attention, concentration, learning, memory, and fine motor speed.

Of 37 patients exposed to the low dose, 21 patients had a statistically significant 30% reduction in pain (placebo vs low: $P = .0069$), as did 22 of 36 patients exposed to the medium dose (placebo vs medium: $P = .0023$), and 10 of 38 patients exposed to placebo. Increasing analgesia was apparent after the second inhalation of vaporized cannabis at 180 minutes, but the treatment had a significant effect at all measured time points—the medium dose more so than the low dose. However, patients were more likely to "feel stoned" with the medium dose.

The adverse effects with both drug doses were negligible, with minimal psychotomimetic effects. Patients on the medium dose performed worse on memory and learning tests; delayed memory was not different between low-dose and placebo groups. Both drug doses affected attention and psychomotor skills. Neuropsychologic effects were of limited duration and readily reversible within 1 to 2 hours.

At the end of each study session, patients were asked to guess which dose they received, and they guessed right most of the time, including 61% of the time for the low dose, 89% of the time for the medium dose, and 63% of the time for the placebo. All guessed the medium dose correctly when it was not given as the first dose. However, the researchers don't feel the "unmasking" of the blinding obviated the conclusion that active study medication resulted in superior analgesia compared with placebo. "The effect of the cannabis treatment on analgesia maintained significance above and beyond any influence of the 15 different side effects," the researchers conclude.

Source: Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. *J Pain.* 2013;14(2):136-148. doi: 10.1016/j.jpain.2012.10.009.

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