Sofosbuvir is administered orally and is unaffected by food. After oral administration, plasma concentrations of sofosbuvir and of its active metabolite peak in 0.5–2 h and 2–4 h, respectively. Approximately 61–65% of sofosbuvir is bound in plasma proteins, but very little of the active metabolite is bound. Both sofosbuvir and its active metabolite are cleared renally, with $t_{1/2}$ values of 0.4 h and 27 h, respectively. Sofosbuvir is relatively free from clinically significant drug interactions, although P-glycoprotein inducers can reduce sofosbuvir concentrations.

Sofosbuvir is generally well tolerated and has not been associated with significant toxicity. The most common side effects in recipients of sofosbuvir have been attributable to concomitant administration of IFN and ribavirin in combination clinical trials (see below).

Sofosbuvir has been studied in a variety of controlled and open-label clinical trials. In late 2013, the results of these trials led to its recommendation—in triple combination with pegylated IFN and ribavirin—as first-line treatment for chronic hepatitis due to HCV genotypes 1, 4, 5, and 6, in which SVRs among treatment-naïve patients were 89–97%. For HCV genotypes 2 and 3, IFN-free regimens consisting of sofosbuvir and ribavirin have been recommended, with SVRs among treatment-naïve patients of 93% for genotype 2 and 61% for genotype 3.

PROTEASE INHIBITORS

BOCEPREVIR, TELAPREVIR

This drug class is specifically designed to inhibit the 3/4A (NS3/4A) HCV protease. These agents resemble the HCV polypeptide and, when processed by the viral protease, form a covalent bond with the catalytic NS3 serine residues, block further activity, and prevent proteolytic cleavage of the HCV polyprotein into NS4A, NS4B, NS5A, and NS5B proteins. Boceprevir and telaprevir are linear ketoamide compounds that are active against HCV genotype 1 (1b > 1a) and much less so against genotypes 2 and 3. These first-generation protease inhibitors received approval for combination therapy (with IFN and ribavirin) for genotype 1 infection. Neither boceprevir nor telaprevir is now recommended for the treatment of hepatitis C. These drugs have been supplanted by sofosbuvir and by simeprevir, a second-generation protease inhibitor with improved pharmacokinetic properties, fewer drug–drug interactions, and less overall toxicity (see below).

SIMEPREVIR

Simeprevir is a second-generation NS3/4A protease inhibitor with antiviral activity against genotype 1 (1b > 1a); the EC_{50} is 9.4 nM in an HCV genotype 1b replicon. The NS3 polymorphism Q80K, which is present in approximately one-third of patients carrying HCV genotype 1b, increases the EC_{50} by elevenfold and results in clinical resistance to simeprevir. Thus, testing for Q80K should be carried out if treatment with simeprevir is being considered. Cross-resistance occurs between simeprevir and the first-generation protease inhibitors boceprevir and telaprevir.

Simeprevir is orally administered as a 150-mg capsule, and its bioavailability is increased by administration with food. The serum concentration peaks 4–6 h after oral administration. The drug's elimination half-life is 10–13 h in healthy individuals and 41 h in patients with hepatitis C. Simeprevir is nearly entirely bound by plasma proteins and cleared by biliary excretion. Because there is no renal excretion, dose adjustments are not required in the presence of renal dysfunction. Simeprevir is metabolized by hepatic CYP3A and therefore should not be used in patients with decompensated liver function.

Because of its metabolism by cytochrome P450 3A (CYP3A), simeprevir interacts with drugs that induce or inhibit CYP3A, and these interactions may concomitantly increase or reduce plasma concentrations of simeprevir. Administration of simeprevir may also increase plasma concentrations of drugs that are substrates for hepatic organic anion-transporting polypeptide 1B1 or 1B3 or for P glycoprotein transporters.

Toxicity observed during clinical trials with simeprevir included photosensitivity (usually mild or moderate) in 28% of recipients and reversible hyperbilirubinemia (both conjugated and unconjugated), which was generally mild to moderate. Most of the other adverse effects that were seen in clinical trials with simeprevir were attributable to concomitant administration of IFN and ribavirin.

Simeprevir has been recommended as a component of alternative treatment—in combination with pegylated IFN and ribavirin—of chronic infection with HCV genotypes 1 and 4. Daily simeprevir, daily ribavirin, and weekly pegylated IFN for 12 weeks followed by another 12 weeks of pegylated IFN and ribavirin resulted in an SVR of 80% in the absence of the Q80K variant. In general, simeprevir-based triple therapy appeared to be 10% less likely to yield an SVR than sofosbuvir-based therapy and more likely to cause adverse effects. However, for prior nonresponders or partial responders to pegylated IFN, the IFN-free regimen of simeprevir, sofosbuvir, and ribavirin shows promise.

INVESTIGATIVE AGENTS OF INTEREST

Next-generation direct-acting antivirals against HCV inhibitors are under active development. These agents include second-generation inhibitors of NS3/4, NS5B polymerase inhibitors, and inhibitors of NS5A (a membrane-associated phosphoprotein that is part of the HCV RNA replication complex). These investigational agents are making progress toward IFN-free regimens, shorter courses of therapy, improved tolerability, and reduction of resistance. For updated information, readers should consult *http://www.hcvguidelines.org/*.