for telaprevir, 12 weeks of triple-drug therapy (PEG IFN, ribavirin, telaprevir), followed by 36 weeks of PEG IFN–ribavirin therapy. In preliminary trials among HIV-HCV co-infected patients, telaprevir-based triple-drug therapy (independent of whether they were receiving antiretroviral therapy [no antiretroviral drugs, efavirenz-tenofovir-emtricitabine, or ritonavir-boosted atazanavir-tenofovir-emtricitabine or lamivudine]) resulted in an SVR in 28 of 38 patients (74%), compared with 10 of 22 control patients (45%) treated with PEG IFN–ribavirin (60 study subjects); boceprevir-based triple-drug therapy (all were also receiving antiretroviral therapy) resulted in an SVR in 40 of 64 patients (63%), compared with 10 of 34 control patients (29%) treated with PEG IFN–ribavirin (98 study subjects). Thus, for the prior standard of care, PEG IFN plus ribavirin, although the likelihood of an SVR is lower for HIV-HCV co-infected patients than for HCV-monoinfected patients, for protease inhibitor–based regimens, rates of SVR are comparable in HIV-HCV co-infected and HCV-monoinfected patients.

In HCV/HIV-infected patients, ribavirin can potentiate the toxicity of didanosine (e.g., lactic acidosis) and the lipoatrophy of stavudine, and zidovudine can exacerbate ribavirin-associated hemolytic anemia; therefore, these drug combinations should be avoided.

Patients with a history of injection drug use and alcoholism can be treated successfully for chronic hepatitis C, preferably in conjunction with drug and alcohol treatment programs. Because ribavirin is excreted renally, patients with end-stage renal disease, including those undergoing dialysis (which does not clear ribavirin), are not ideal candidates for ribavirin therapy. Rare reports suggest that reduced-dose ribavirin can be used, but the frequency of anemia is very high, and data on efficacy are limited. If patients with renal failure (glomerular filtration rate <60 mL/min) are treated, the PEG IFN-α2a dose should be reduced from 180 to 135 μg weekly and the PEG IFN-α2b dose reduced from 1.5 to 1 μg/kg weekly; similarly, the daily ribavirin dose in this population should be reduced to 200–800 mg (but not used or used cautiously at very low doses) if hemodialysis is required. Neither the optimal regimen nor the efficacy of therapy is well established in this population.

NOVEL ANTIVIRALS*

To date, attempts to develop better-tolerated ribavirin successors or improved types of IFN-α or longer acting IFNs than PEG IFN have not been successful. The demonstration that responsiveness to antiviral therapy is influenced by genetic variation in *IL28B*, which codes for IFN-λ (as noted above), raises the possibility that IFN-λ might be an effective or even more effective IFN for treating hepatitis C; early trials are in progress, but elevations of aminotransferase levels in treated subjects have raised concerns and delayed development. Beyond telaprevir and boceprevir, other direct antivirals that target HCV polymerase, protease, or NS5A (a membrane phosphoprotein component of the viral replication complex) are being investigated, as well as agents that can target host-encoded proteins. Among the novel antivirals are drugs with improved pharmacokinetic and resistance profiles, less treatment complexity, pangenotypic activity, fewer side effects, and fewer drug-drug interactions.* The pace of successful trials of all-oral regimens has accelerated. All-oral combinations of a second-generation protease inhibitor (asunaprevir) plus an NS5A inhibitor (daclatasvir); of a uridine nucleoside polymerase inhibitor (sofosbuvir)* plus ribavirin; of a polymerase inhibitor (sofosbuvir) plus an NS5A inhibitor (ledipasvir or daclatasvir) and ribavirin; and of combinations of a ritonavir-boosted protease inhibitor (ABT-450) plus a nonnucleoside polymerase inhibitor (ABT-333) plus an NS5A inhibitor (ABT-267) with or without ribavirin have been studied in clinical trials. Several of these drug combinations have achieved SVR rates exceeding 90%, even approaching 100%, for both treatment-naïve and treatment-experienced patients (including patients who failed to respond to first-generation protease inhibitors), across all HCV genotypes and independent of host *IL28B* genotype, and with treatment durations of 12–24 weeks or even shorter (8 weeks). Potentially, as early as 2014 or 2015, such combinations of direct antiviral agents will be used in drug cocktails that may replace IFN-based regimens entirely.

Less advanced is development of inhibitors of host proteins, such as oral, nonimmunosuppressive inhibitors of cyclophilin A (which interacts with NS5A during HCV replication) and subcutaneous antisense antagonists of host liver-expressed micro-RNA-122 (which promotes HCV replication). Given the accelerated progress of all-oral, short-treatment-duration, high-efficacy, direct-acting antivirals, these alternative approaches may not be practical or competitive.

AUTOIMMUNE HEPATITIS

DEFINITION

Autoimmune hepatitis is a chronic disorder characterized by continuing hepatocellular necrosis and inflammation, usually with fibrosis, which can progress to cirrhosis and liver failure. When fulfilling criteria of severity, this type of chronic hepatitis, when untreated, may have a 6-month mortality of as high as 40%. Based on contemporary estimates of the natural history of autoimmune hepatitis, the 10-year survival is 80–98% for treated and 67% for untreated patients. The prominence of extrahepatic features of autoimmunity and seroimmunologic abnormalities in this disorder supports an autoimmune process in its pathogenesis; this concept is reflected in the prior labels *lupoid* and *plasma cell hepatitis*. Autoantibodies and other typical features of autoimmunity, however, do not occur in all cases; among the broader categories of "idiopathic" or cryptogenic chronic hepatitis, many, perhaps the majority, are probably autoimmune in origin. Cases in which hepatotropic viruses, metabolic/genetic derangements (including nonalcoholic fatty liver disease), and hepatotoxic drugs have been excluded represent a spectrum of heterogeneous liver disorders of unknown cause, a proportion of which are most likely autoimmune hepatitis.

IMMUNOPATHOGENESIS

The weight of evidence suggests that the progressive liver injury in patients with autoimmune hepatitis is the result of a cell-mediated immunologic attack directed against liver cells. In all likelihood, predisposition to autoimmunity is inherited, whereas the liver specificity of this injury is triggered by environmental (e.g., chemical, drug [e.g., minocycline], or viral) factors. For example, patients have been described in whom apparently self-limited cases of acute hepatitis A, B, or C led to autoimmune hepatitis, presumably because of genetic susceptibility or predisposition. Evidence to support an autoimmune pathogenesis in this type of hepatitis includes the following: (1) In the liver, the histopathologic lesions are composed predominantly of cytotoxic T cells and plasma cells; (2) circulating autoantibodies (nuclear, smooth muscle, thyroid, etc.; see below), rheumatoid factor, and hyperglobulinemia are common; (3) other autoimmune disorders—such as thyroiditis, rheumatoid arthritis, autoimmune hemolytic anemia, ulcerative colitis, membranoproliferative glomerulonephritis, juvenile diabetes mellitus, celiac disease, and Sjögren's syndrome—occur with increased frequency in patients and in their relatives who have autoimmune hepatitis; (4) histocompatibility haplotypes associated with autoimmune diseases, such as HLA-B1, -B8, -DR3, and -DR4 as well as extended haplotype *DRB1*0301* and *DRB1*0401* alleles, are common in patients with autoimmune hepatitis; and (5) this type of chronic hepatitis is responsive to glucocorticoid/immunosuppressive therapy, effective in a variety of autoimmune disorders.

Cellular immune mechanisms appear to be important in the pathogenesis of autoimmune hepatitis. In vitro studies have suggested that in patients with this disorder, $CD4^+$ T lymphocytes are capable of becoming sensitized to hepatocyte membrane proteins and of destroying liver cells. Molecular mimicry by cross-reacting antigens that contain epitopes similar to liver antigens is postulated to activate these T cells, which infiltrate, and result in injury to, the liver. Abnormalities of immunoregulatory control over cytotoxic lymphocytes (impaired regulatory CD4+CD25+ T cell influences) may play a role as well. Studies of genetic predisposition to autoimmune hepatitis demonstrate that certain haplotypes are associated with the disorder, as enumerated above,