In the Literature

Management of Acute Hepatitis C Virus Infection


The management of patients acutely infected with hepatitis C virus (HCV) is premised on several factors. Many patients, as many as 50% in some series, will spontaneously clear the infection. On the other hand, the only available treatment until recently involved the prolonged administration of pegylated interferon-α together with ribavirin, a regimen that for most patients is onerous. Nonetheless, this regimen has been very effective in the treatment of acute HCV infection—much more effective than it is in chronically infected individuals. Taking these issues into consideration, current guidelines generally recommend observing acutely infected patients for 12 weeks before initiating treatment in those who fail to spontaneously clear their infection within this time. The ability to accurately predict viral clearance and select optimal candidates for treatment would therefore be of value.

Beinhardt and colleagues examined a series of variables utilizing a data set involving 136 adult patients [1]. Candidate variables identified were presence of IL28B, age ≥35 years, peak bilirubin ≥6 mg/dL, HCV RNA decline >2.5 log10 by 4 weeks, serum interferon-γ–induced protein 10 (IP-10) ≥546 pg/mL, and presence of CD4+ T-helper type 1 cells. A scoring system utilizing these factors was devised in this derivation study but obviously require evaluation in a validation cohort.

Mangia and colleagues evaluated 169 patients with acute HCV infection. Almost two-thirds were male; the mean age of the entire cohort was 44.0 years. Their mean serum alanine aminotransferase concentration at the time of diagnosis was 1329 ± 972 IU/mL, and this value proved to be higher in those with spontaneous clearance than in those with persistent infection. IL28B analysis found that 94 (56%) were CC homozygous, 6% were homozygous for TT, and the remaining 38% were heterozygous.

Spontaneous viral clearance occurred in 28% of the 169 patients evaluated. Multiple HLA DRB1 and DQB alleles were examined, but none correlated with spontaneous clearance, whereas jaundice and IL28B CC genotype did. Perhaps the most dramatic finding was that the probability that a non-CC patient without jaundice would fail to spontaneously clear their infection was 98%.

Eighty of the 122 (66%) patients without spontaneous viral clearance agreed to treatment with interferon with or without ribavirin that they received for variable durations at the discretion of their care providers. A sustained virologic response (SVR) was achieved in 58 (71.5%), including 65.2% of 40 patients infected with genotype 1 virus. In multivariate analysis, HCV genotype, IL28B genotype, treatment timing (before or after 24 weeks postdiagnosis), adherence to treatment, and use of ribavirin were independent predictors of SVR. Based on their findings, patients with acute HCV infection without jaundice and with IL28B CC/TT genotype should receive early treatment.

Mangia and colleagues provide valuable data that can assist in the management of patients with acute HCV infection. The current flood of novel small therapeutic molecules already available, or in the pipeline, will, however, significantly alter the management equation.

Reference

Serotonin Syndrome: Linezolid vs Vancomycin


Current US Food and Drug Administration (FDA)—approved labeling warns about the potential development of serotonin syndrome in individuals who receive linezolid together with serotoninergic (and adrenergic) drugs such as many widely used antidepressants. This warning is based on the ability of linezolid to weakly inhibit monoamine oxidase as well as case reports of the occurrence of serotonin syndrome in patients receiving such combinations. A review of spontaneous reports to the FDA found only quite limited evidence to indicate this was a significant problem [1]. Butterfield and colleagues subsequently examined the locked databases of 20 clinical trials in which patients were randomized to receive linezolid or a comparator antibiotic—either a glycopeptide or a β-lactam [2, 3]. In these trials, 4265 of 10 484 (40.7%) patients were also receiving a serotonergic agent. The number of patients...
meeting 1 or both of 2 sets of criteria for serotonin syndrome was <10 among both linezolid and comparator recipients, and there was no statistically significant difference between the treatment arms.

Lodise and colleagues have now taken this a step further by examining the incidence of serotonin syndrome in patients receiving linezolid relative to those receiving vancomycin in a “real world” (at least in the context of the Veterans Health Administration) population, as opposed to the highly selected participants entered into clinical trials. They performed an observational matched cohort study in patients hospitalized in the Upstate New York Veterans Affairs Healthcare Network involving 251 patient pairs. The latter were matched by hospital, hospital ward, prior length of stay, age, and baseline platelet count. A natural word searching algorithm was used to examine the electronic medical record for evidence of symptoms suggestive of serotonin syndrome, including those relevant to the Hunter serotonin toxicity criteria (HSTC). Using HSTC, patients must meet at least 1 of the following criteria: spontaneous clonus; inducible clonus plus agitation or diaphoresis; ocular clonus plus agitation or diaphoresis; tremor plus hyperreflexia; hypertonia plus temperature >38°C plus ocular or inducible clonus. Subjects were required to have received linezolid for at least 1 day or vancomycin for 2 days (to account for frequent single-dose administration of this glycopeptide). Excluding the use of antihistamines and antiemetics (reportedly frequently given to counteract side effects of vancomycin), similar proportions in the 2 arms received serotonergic agents—16.7% of vancomycin recipients and 15.9% of those given linezolid.

Searching for terms associated with serotonin syndrome, no patients in either group were found to meet prespecified criteria. With application of HSTC to the entire study group, 3.2% of linezolid recipients and 8.8% of vancomycin recipients met the definition. When stratified by concurrent receipt of a serotonergic medication, these criteria were met by 3.2% and 8.8% of linezolid and vancomycin recipients, respectively. Many patients meeting criteria had preexisting comorbidities that could confound the analysis and, after excluding rigidity from the criteria (many affected had known Parkinson’s disease), only 4 (0.15%) linezolid recipients and 11 (0.44%) of those given vancomycin met criteria.

This study adds to the very reasonable conclusion that the risk of development of the serotonin syndrome in patients receiving linezolid relative to that seen with vancomycin use is very limited. Furthermore, even when it occurs (and is recognized), it most often resolves within 24 hours of discontinuation of the precipitating agents, although this may take longer after stopping administration of drugs with long serum half-lives.

References


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