

Pediatric Subcommittee
of the
Anti-Infective Drugs Advisory Committee
Center for Drug Evaluation and Research, Food and Drug Administration
April 23, 2001
Issue: Treatment of Chronic Hepatitis C in Children

Questions for the Subcommittee

1. Treatment of HCV infection in adults raises concern about the relatively low rates of success and the durability of response; lack of information on the impact of therapy on long-term outcomes such as cirrhosis and hepatocellular carcinoma; as well as known and unknown toxicities.

Given these concerns, please discuss the need for and the appropriate timing during drug development of agents developed to treat Hepatitis C infections in the pediatric population.

2. As previously noted, the 1994 Pediatric Rule allows extrapolation of adult efficacy data to the pediatric population when the disease and response to therapy are sufficiently similar in adults and children. Determination of when extrapolation is appropriate can be difficult and controversial.

Please discuss whether the course of hepatitis C infections and the response to therapy are likely to be sufficiently similar to allow the extrapolation of adult efficacy data to the pediatric population. In your discussion, please consider the following:

- the small number of pediatric patients available for enrollment in clinical studies; and
- the potential role for exposure/response studies.

In addition, should it be determined that extrapolation of efficacy data from adults infected with Hepatitis C to the Hepatitis C-infected pediatric population may be appropriate, please comment on the following:

- Identification of subgroups of pediatric patients whose disease may be sufficiently different such that extrapolation would not be appropriate?
- The basis for and identification of those children whose HCV infection should be treated and therefore could reasonably be included in a clinical trial;
- Study designs that may provide for the optimal collection of safety, pharmacokinetic, and activity data.
- Need for and choice of control group; optimal duration of treatment; appropriate activity endpoints (HCV RNA, liver biopsy).

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Questions for the Subcommittee (cont.)

3. The marketed treatments for Hepatitis C infection in adults include Polyethylene glycol (PEG) conjugated to interferon, various non-PEG interferons, and combination therapy consisting of Intron-A and Ribavirin (Rebetron). The data to support an indication for PEG interferon plus Ribavirin in adults have recently been submitted to the agency; preliminary results suggest marginally higher response rates but possibly more safety concerns such as more severe neuropsychiatric events, bone marrow suppression, thyroid disorders, and cardiovascular events.

No products are currently approved for the treatment of Hepatitis C infection in pediatric populations. Studies with Rebetron are underway; interim pharmacokinetic and safety data have recently been submitted to the agency. The interferon manufacturers are interested in studying the combination of PEG interferon + ribavirin (but not PEG interferon monotherapy) in pediatric patients.

- Are additional studies of interferon-based therapies in pediatric patients warranted at this time?

If yes,

- Should only combination therapy (PEG-interferon + Ribavirin) be studied, or is it appropriate to also evaluate PEG interferon monotherapy in pediatric patients?
4. The long-term follow-up of both adult and pediatric patients who have received treatment for Hepatitis C infection is needed to address the impact of therapy on the clinical endpoints of cirrhosis, hepatocellular carcinoma, and mortality.
 - Please discuss approaches intended to maximize the collection of long-term follow-up data in pediatric patients who have been enrolled in clinical trials of therapies for Hepatitis C. Issues that might be addressed include identification of those who should receive follow-up, the duration of follow-up, and parameters to be followed.
 5. Please provide recommendations for additional areas of research that should be undertaken to expand the data on Hepatitis C infections in infants and children.