Prospective evaluation of primary infection due to HCV, HGV or TTV in children with newly diagnosed neoplasia

**Hepatitis C virus (HCV), hepatitis G virus (HGV) and transfusion-transmitted virus (TTV) infections have been described in poly-transfused patients.[1] In this prospective study to determine the incidence of these infections in children with newly diagnosed neoplasia, HCV was absent, while TTV and HGV were observed.**

Children admitted to G. Gaslini Children's Hospital Genoa, Italy for a newly diagnosed neoplasia from March 1997 to September 1998, and never previously transfused were prospectively evaluated for development of any liver disease, defined as alanine-aminotrasferase (ALT) levels more than 1.5 above normal values. Blood samples were prospectively collected at the time of the first observation and every 3 months or at the time of liver disease. Collected samples were subsequently tested for presence of viral genome. All patients had a minimum of 4 samples analyzed.

Detection of HCV-RNA, HGV-RNA and TTV-DNA was performed by polymerase chain reaction (PCR). HCV-RNA was amplified by using a nested PCR method with four primers complementary to the highly conserved 5' non-coding region of the HCV genome.[2] HGV-RNA was subjected to PCR using specific primers for the NS3 and the 5'-UTR genome regions in all serum samples.[3] TTV-DNA was amplified by semi-nested PCR with TTV-specific primers derived from two conserved regions according to the published sequences.[4]

Twenty-six children (16 males and 10 females) with a median age of 5 years (range 3-15), were followed for a median of 36 months (range 12-48) after the beginning of antineoplastic chemotherapy.

Underlying diseases were acute lymphoblastic leukemia (n=18), acute myelogenous leukemia (n=1), non-Hodgkin's lymphoma (n=2), Ewing's sarcoma (n=3), Wilms' tumor (n=1) and neuroblastoma (n=1). All patients received antineoplastic protocols approved by the *Italian Association of Pediatric Hematology and Oncology*.

At baseline no HCV, HGV or TTV genome was detected in plasma. During follow-up, HCV infection was never detected. A primary viral infection was observed in 8/26 (31%) patients, after a median of 15 months (range 6-24): TTV in 6/26 (23%), HGV in 1/26 (4%), TTV-HGV co-infection in 1 (4%), without epidemic clusters. Clinical data are summarized in Table 1.

An increase in ALT levels was present in 2 patients at first observation and in 14/26 (54%) during follow-up. At documentation of primary viral infection 5 patients (4 TTV and 1 TTV-HGV co-infection) had ALT abnormalities, while the remaining 3 (2 TTV and 1 HGV) had normal values. ALT values were normal a median of 23.5 months (range 17-33) after documented infection, after discontinuation of antineoplastic therapy.

A median of 9.5 (range 7-18) transfusions were given before TTV documentation, 49 before HGV and 15 before HGV-TTV. The patients with TTV infection received a median of 6 (range 4-11) packed red blood cell (p-RBC) units and a median of 2 (range 0-12) platelet units from apheresis.

No statistically significant difference ($p$=0.41, t-test for independent data) was observed in the number of transfusions administered to infected and non-infected patients (data not shown).

None of our patients developed HCV infection, while 31% acquired TTV and/or HGV. The absence of HCV confirms the efficacy of blood donor selection.

TTV and HGV have been detected worldwide with different frequencies both in children and adults with or without chronic liver disease and with or without a history of transfusions.[5-7] In Italian children, TTV and HGV have been reported as co-infection with HCV.[8,9] In our series, p-RBC were transfused more frequently in patients with TTV, at least indirectly confirming an observation in Italian adults with transfusion-dependent thalassemia.[10]

Increased ALT values, observed in 54% of our patients, did not represent a marker of primary viral infection and all patients had normal ALT values after discontinuation of antineoplastic chemotherapy.

At present, the true clinical significance of HGV and TTV infection is unknown, and controversies exist about whether these viruses are primary hepatitis viruses and whether or not they cause liver disease.[1,3,4,5-9] However, since HGV and TTV persists for a long time in plasma,[5-8] the late effects of these persistent infections in children who survive a neoplastic disease are unknown and only a very long follow-up will be able to give an answer to this question.

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**Table 1. Clinical characteristics of the patients with TTV and HGV infection.**

| Patients' initials | Detected virus | Months of chemotherapy at diagnosis of viral infections | Number of transfusions before first viral detection | ALT values (IU/L) at time of first viral detection | Last follow up: months after diagnosis of neoplasia | ALT values (IU/L) at time of last observation |
|---|---|---|---|---|---|---|
| AS | TTV | 9 | 7 | 96 | 42 | 14 |
| CL | TTV | 19 | 8 | 110 | 44 | 13 |
| RM | TTV | 20 | 18 | 12 | 42 | 8 |
| TS | TTV | 6 | 10 | 76 | 33 | 17 |
| GD | TTV | 9 | 28 | 107 | 37 | 19 |
| PA | TTV | 11 | 9 | 35 | 29 | 12 |
| TM | TTV/HGV | 19 | 15 | 258 | 36 | 17 |
| FJ | HGV | 24 | 49 | 48 | 45 | 52 |

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