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Mitigation of Hepato-Cellular Injury Caused by HAART with Glycyrrhizin Compound in Patients Co-Infected with HIV and HCV

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Hepato-cellular injury occurring several weeks after initiation of highly active anti-retroviral therapy (HAART) against HIV infection is not infrequent. In most cases, increase of serum alanine aminotransferase (ALT) is transient and it decreases spontaneously without any treatment. However, some patients dually infected with HIV and hepatitis virus are obliged to discontinue HAART because of moderate or severe hepato-cellular injuries (1,2). In our hospital, 48 out of 270 patients who had been receiving protease inhibitors since 1997 developed high serum ALT level (increase by more than three-fold of basal values and/or more than 200 IU/L [normal range 0-30]).

Incidence of the hepatitis C virus (HCV) infection is relatively high in Japan; almost all Japanese HIV-infected hemophiliacs have tested positive for antibodies to HCV. Currently, a glycyrrhizin compound Stronger-neo-Minophagen C (SNMC) is widely used to treat hepato-cellular injury in all patients with HCV. Glycyrrhizin is reported to have a protective effect on hepatocyte (3). SNMC consists of 0.2% glycyrrhizin, 0.1% cysteine, and 2.0% glycine in physiologic saline, and has been approved by the Ministry of Health and Welfare of Japan in the treatment for chronic hepatitis. Here we report a successful mitigation of HAART-induced hepato-cellular injury with SNMC without reduction or discontinuation of any anti-HIV drugs.

Four hemophiliacs (cases 1-4), dually infected with HIV and HCV, had moderate hepato-cellular injury after initiation of HAART (stavudine, lamivudine, and protease inhibitors). Their ALT levels were mildly elevated before HAART, indicating that they had chronic active hepatitis. They had nausea and general malaise, and showed further increase of ALT; more than 280 to 480 IU/L within 5 weeks after initiation of HAART (case 2, 14 weeks later). Cases 1 and 3 had to discontinue HAART as a result of hepato-cellular injury.

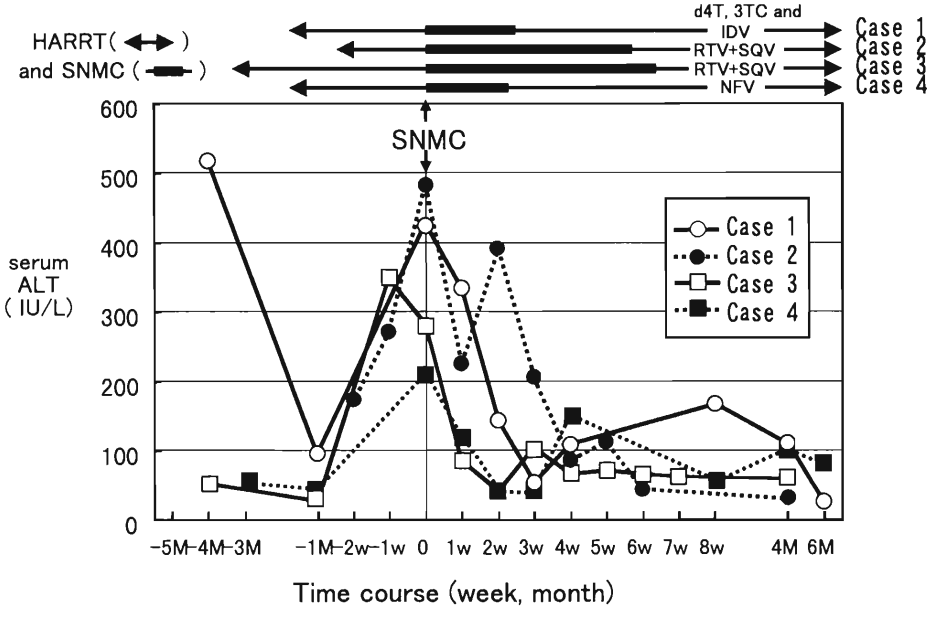

Figure. Clinical course of patients.
d4T; stavudine, 3TC; lamivudine, IDV; indinavir, RTV; ritonavir, SQV; saquinavir, NFV; nelfinavir

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These patients were then hospitalized and administered with SNMC intravenously, and HAART was reinitiated after we had obtained informed consent.

Daily administration of SNMC was started with initial doses of 40 to 80 ml and gradually tapered with careful monitoring of ALT. SNMC was administered for 16 to 46 days. Clinical complaints disappeared from all of these patients within 10 days, and serum ATL values immediately declined, reaching less than 100 IU/L within 4 weeks (Fig.). As a consequence, all of these patients were able to continue HAART without reducing any anti-HIV drugs. Although ALT of all patients did not stay within the normal limit, further elevation of ALT was not observed up to 4 months after completion of SNMC. No side effects, such as the pseudo-aldosteronism often induced by the glycyrrhizin (3) in SNMC, were observed. Evaluation of HCV viral load showed no significant changes such as those observed in other HCV (+) / HIV (–) patients. HIV-1 viral load was suppressed to less than 200 copies/ml within 2 months in cases 2, 3, and 4, and was decreased to 4400-2200 copies/ml within 4 weeks in case 1, indicating that HIV-1 viral load was adequately suppressed in all clinical courses. In addition, another hemophiliac patient who showed persistent elevation in serum ALT for 5 months after discontinuation of previous HAART (AZT, ddC, and SQV), was administered with SNMC. His ALT had declined to 335-61 IU/L within 19 days, and he was able at that time to reinitiate another HAART regimen (d4T, 3TC, and RTV). His ALT level remained lower than 96 IU/L for the following 6 months.

The precise action mechanism of SNMC is still unclear. However, SNMC is very popular, largely because its efficacy has been confirmed by many Japanese physicians through the traditional treatment of liver dysfunction in Japan. Hepato-cellular injury after HAART can be caused by three possible mechanisms; side effects by HAART itself, exacerbation of HCV hepatitis, and transient local immune response to HCV in the course of immune reconstitution (4). The cause of the hepato-cellular injury in these four cases was unclear. However, the third mechanism is most likely because there were no significant increases of HCV viral load nor any signs of exacerbation of HCV hepatitis in any patients. SNMC is cost-effective and has a low toxicity. This limited pilot study indicated that a larger clinical trial is warranted for cases suffering from hepato-cellular injury as a result of HAART.

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