PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

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This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Hepatitis B viral growth associated with the use of drugs with immunosuppressive effects

Hepatitis may occur due to hepatitis B viral growth in hepatitis B virus carriers (including patients negative for HBs antigen) who were administered drugs with immunosuppressive effects such as immunosuppressants, antineoplastic agents, and antirheumatic agents. An alert has been issued to monitor the results of liver function tests or hepatitis viral markers. However, cases of hepatitis B viral growth, some of which became fulminant, have been reported.

When administering these drugs, Healthcare professionals should carefully observe patient's signs and symptoms related to hepatitis B viral growth by monitoring results of liver function tests or hepatitis viral markers.

Case summaries

(Case 1) A female patient in her 20s with myelodysplastic syndrome

Anti-HBs antibody was 10000 mIU/mL before the stem cell transplantation. After the transplantation, immunosuppressants ciclosporin and methotrexate were administered for 15 months. One month after the treatment with immunosuppressants was completed, anti-HBs antibody decreased to below 10 mIU/mL. Two months after the treatment with immunosuppressants was completed, HBV-DNA increased to 4.4 Log copy/mL and AST increased up to 207 U/L, and hepatitis B developed.

(Case 2) A male patient in his 40s with non-Hodgkin's lymphoma

The test performed before starting the treatment with antineoplastic agents showed HBs antigen (+), HBs antibody (-), HBc antibody (+), HBe antigen (-), HBe antibody (+) and HBV-DNA 3.9 LGE/mL. The patient underwent 3 cycles of combination therapy with rituximab and THP-COP. At 94 days after completion of rituximab, the patient had general malaise and anorexia. The test showed significant hepatic dysfunction (AST 2358 U and ALT 3106 U). The patient was admitted to the hospital. The patient was diagnosed severe hepatitis resulted from acute exacerbation of hepatitis B, G-I therapy and administration of lamivudine were started. The test performed at 95 days after completion of rituximab treatment and showed HBV-DNA over 8.7 LGE/mL. The hepatitis subsequently became fulminant. The patient died of fulminant hepatitis at 106 days after completion of rituximab.

[Excerpted from RITUXAN Injection 10 mg/mL Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter), December 2006 (information partially modified)]

(Case 3) A male patient in his 50s with rheumatoid arthritis
The test showed HBs antigen (+), HBe antigen (-), HBe antibody (+) and HBV-DNA 3.1 Log copy/mL. Etanercept and tocilizumab had been administered prior to the treatment with adalimumab. Prednisolone and salazosulfapyridine were concomitantly used at the start of adalimumab treatment. At 167 days after initiation of adalimumab treatment, taclolimus and methotrexate were added to the treatment. At 279 days after initiation of adalimumab treatment, the antirheumatic treatment was completed. At 8 days after completion, the patient had anorexia, upper abdominal pain and pyrexia. At 13 days after completion, fulminant hepatitis (AST 1257 IU/L and ALT 2594 IU/L) developed. The test performed at 16 days after completion showed HBe antigen (s/co level) < 0.5; HBe antibody 99% and HBc antibody (s/co level) 7.55. The patient was admitted to the hospital with jaundice and PT prolongation. The liver function did not improve despite continuous hemodiafiltration, plasma exchange, steroid pulse therapy and administration of entecavir. The patient died at 33 days after completion of antirheumatic treatment.

* It should be noted that other than the drugs involved in the 3 cases presented above, similar cases involving drugs with immunosuppressive properties have been reported.

Healthcare professionals should be aware of drugs with immunosuppressive effects that may also induce onset, recurrence, or aggravation of infections other than hepatitis B.

Related information

- The Health and Labour Sciences Research Grants, The Research Project of Emergency Strategy for the Conquest of Hepatitis, etc. has released a report “Clarification of current status for reactivation of hepatitis B virus associated with immunosuppressants and antineoplastics and establishment of the preventive measures.” You can find it in the database on the Health and Labour Sciences Research website (http://mhlw-grants.niph.go.jp/niph/search/NIST00.do) (in Japanese).
- The Japan College of Rheumatology issued “The proposal for management of rheumatic disease patients with hepatitis B virus infection receiving immunosuppressive therapy” (http://www.ryumachi-jp.com/info/news110906.html) (in Japanese).

About this information

* “PMDA Alert for Proper Use of Drugs” communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the Pharmaceutical Affairs Law.
* We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future.
* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibilities on them, but is provided to promote the proper use of drugs.

Active ingredients with immunosuppressive properties

(Alerts against hepatitis B virus growth provided in the package insert) (As of September 2011)

	Nonproprietary name
Immunosuppressants	Azathioprine
	Everolimus
	Gusperimus Hydrochloride
	Anti-human Thymocyte Immunoglobulin, Rabbit
	Ciclosporin
	Tacrolimus Hydrate
	Basiliximab (Genetical Recombination)
	Mycophenolate Mofetil
	Mizoribine
	Muromonab-CD3
Antineoplastic agents	Everolimus
	Fludarabine Phosphate
	Methotrexate
	Rituximab (Genetical Recombination)
Antirheumatic agents	Adalimumab (Genetical Recombination)
	Abatacept (Genetical Recombination)
	Infliximab (Genetical Recombination)
	Etanercept (Genetical Recombination)
	Golimumab (Genetical Recombination)
	Methotrexate

	Nonproprietary name
Steroids	Cortisone Acetate
	Dexamethasone
	Dexamethasone Sodium *m*-sulfobenzoate
	Dexamethasone Palmitate
	Dexamethasone Sodium Phosphate
	Triamcinolone Acetonide
	Triamcinolone
	Hydrocortisone Sodium Phosphate
	Hydrocortisone
	Hydrocortisone Sodium Succinate
	Fludrocortisone Acetate
	Prednisolone
	Prednisolone Sodium Succinate
	Prednisolone Sodium Phosphate
	Betamethasone/d-Chlorpheniramine Maleate
	Betamethasone Sodium Phosphate
	Betamethasone Acetate/Betamethasone Sodium Phosphate
	Betamethasone
	Methylprednisolone
	Methylprednisolone Sodium Succinate
	Methylprednisolone Acetate

* Healthcare professionals should report any similar cases involving active ingredients with immunosuppressive properties not listed above to the Drug and Medical Device Safety Information Reporting System.

Information on the package insert of active ingredients with immunosuppressive properties is available at the Pharmaceuticals and Medical Devices Information Website (in Japanese).
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html

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