Guidelines for the Prevention of HBV Reactivation during Immunosuppressive Therapy

Circulation to: Departments of Gastroenterology, WYHN
Suggest GI departments share with:
Dept. of Immunomodulatory Therapy, Chapel Allerton Hospital, Departments of Haematology, Oncology, Infectious diseases and Rheumatology locally

Introduction
Hepatitis B infection is becoming increasingly common in the UK due to immigration for areas of high prevalence. E.g., Prevalence in SE Asia is 8-10% of population, Southern Europe and Middle East 2-7%. Patients who are positive for surface antigen (HBsAg +ve) may be “inactive carriers” or may have active liver disease or even cirrhosis, irrespective of their e Antigen status. In addition, patients who appear to have immunologically cleared the virus and are core antibody positive (HBcAb +ve) although surface antigen negative, may harbour virus (“occult infection”) capable of reactivating at times of immunosuppression. Flares of HBV or reactivation of HBV can lead to acute hepatitis, fulminant liver failure and death, or can lead to early cessation or interruption of chemotherapy regimes making them less effective. Prevention of such episodes is therefore desirable.

Reactivation Hepatitis
During immunosuppression virus escapes immune control and starts replicating. The more intensive the immunosuppressive regime, the more this is likely to occur. As treatment is withdrawn and immune reconstitution occurs, recognition of viral antigen provokes reactivation hepatitis which can be fatal. The majority of such cases occur in HBsAg positive patients. However, there is a small but definite risk in sAg-ve patients who are cAb positive due to occult infection. Again, greater immunosuppression leads to greater risk.

There are several reports describing reduction in cases using anti-viral prophylaxis starting at least 1 week prior to chemotherapy and continuing for at least 6 -12 months after cessation of chemotherapy. At time of withdrawing anti-viral prophylaxis there remains a small risk of reactivation and therefore withdrawal is best supervised by a team with specialist knowledge of HBV. This will most usually be a gastroenterology, hepatology or infectious diseases team.

With replication, HBV DNA rises. 2-3 weeks later there is a rise in AST/ALT and the DNA starts to fall. It is possible that at a time of fulminant hepatitis and liver failure DNA may actually be undetectable. Therefore there is a rationale in knowing serological status prior to starting any immunosuppressive therapy even if prophylaxis is not indicated.

Many laboratories will only routinely check for sAg as a screening test. Therefore sAg and cAb must be specifically requested for these patients.

Risk
The risk of reactivation hepatitis is greatest in patients undergoing bone marrow transplant, haematopoietic stem cell transplants, solid organ transplants and chemotherapy for haematological malignancies, especially
where the chemotherapy regime incorporates steroids. In lymphoma patients who are sAg+ve the risk of reactivation is around 38-48%. In bone marrow transplant patients the risk is around 50%. Of these around 10-20% will become jaundiced, and of those between 4-40% will die. Men and younger patients are probably more at risk, as are those with underlying cirrhosis. It is not known if eAg status confers a greater risk.

The risk in other cancers is less well established. Reactivation has been described in breast cancer, nasopharyngeal cancers, lung cancer, pancreatic cancers and HCC.

There are several case reports of reactivation during infliximab therapy and reactivation is also described in rituximab monotherapy.

For short course steroids alone or other immunosuppressive agents such as azathioprine or methotrexate the risk exists but appears to be much lower, and the hepatitis less severe, although fatalities may occur if undiagnosed cirrhosis co-exists.

Prophylaxis vs Treatment

The guidelines have been drawn up to encourage health professionals to look for HBV status prior to planning chemotherapy so that timely treatment can be started. They should also allow anti-viral therapy to be instigated as prophylaxis without delay to cancer treatment with a pathway for referral to a specialist team. In SJUH this would be the hepatologists, but in other hospitals the service may be run by the gastroenterologists or infectious disease specialists.

It is important to understand that some sAg+ve patients will actually need treatment rather than prophylaxis. In such cases lamivudine monotherapy is unlikely to be enough. The referral pathway to discussion with a hepatologist of such patients (sAg+ve, with abnormal LFTs – any level of abnormality +/- or detectable DNA) is highlighted.

Prophylaxis for cAb +ve patients is probably only needed in patients undergoing the most intensive immunosuppression.

Monitoring and Compliance

Monitoring of patients found to be sAg +ve during any immunosuppressive course is important regardless of whether they are on prophylaxis or not. LFTs are probably sufficient but must be followed up with a DNA if become abnormal. Abnormal LFTs during intensive regimes are not uncommon, from many other causes, so numerous, repeated DNA is not needed if this initial follow-up DNA is undetectable, unless there is a strong clinical indication. Such cases are probably best discussed with a hepatologist.

All patients should have an explanation of reporting symptoms of hepatitis – RUQ discomfort, flu-like symptoms or jaundice early. Patients on prophylaxis should be encouraged with full compliance as resistance can emerge rapidly with incomplete suppression of virus levels.
Key Recommendations

Screen all patients undergoing bone marrow transplant, haematopoietic stem cell transplant, solid organ transplant, intensive chemotherapy or rituximab for haematological malignancies eg lymphoma, AML, ALL for HBsAg and HBcAb. Prophylaxis recommended if either found.

Screen all patients undergoing cancer chemotherapy for other solid cancers eg breast, HCC, pancreatic, nasopharyngeal, and immunotherapy eg rituximab monotherapy or infliximab for HBsAg, HBcAb. Prophylaxis recommended if sAg positive, LFT monitoring if cAb positive.

Screen selected high risk patients undergoing immunosuppressive therapy eg corticosteroids, methotrexate, azathioprine for rheumatological etc conditions. High risk patients include homosexual men, IVDUs ethnic origin SE Asia, Eastern or southern Europe, Middle East, Sub-Saharan Africa.

* Screening and prophylaxis in patients undergoing liver transplantation is covered elsewhere in the liver transplant literature and will be guided by the transplant team.

Ref:
Kohrt HE et al. APT 2006;24:1003-1016
Martyak LA et al. Liver International 2007; (e-pub ahead of print)

RJ/MAA 2008
Algorithm for Prevention of HBV Reactivation in Patients undergoing Immunosuppressive Regimes

BMT, stem cell Tx, chemo for lymphoma or other intensive regimes for haematological malignancy, rituximab therapy with steroids, solid organ transplant (except liver)

- sAg +ve +/or cAb +ve
  - Check HBV DNA + LFTs
  - cAb +ve only undetectable DNA normal LFTs
    - Commence lamivudine 100mg daily prior to starting treatment. (dose reduce if renal impairment)
    - Monitor LFTs monthly (unless more frequently needed for chemo etc).
    - If ALT/AST or bilirubin rise, measure DNA urgently and refer to hepatologist urgently.
    - Refer to hepatologist at end of treatment to supervise withdrawal of antiviral treatment at 6-12 months after end of therapy and for monitoring 6-12 months after.
    - LFTs 2 weekly by GP after stopping lamivudine for 12 weeks.

Solid cancer chemotherapy.
(Risk highest if incorporates glucocorticoid therapy)
- Infliximab, rituximab monotherapy

- sAg +ve +/or cAb +ve
  - Check HBV DNA + LFTs
  - detectable DNA Abnormal LFTs
    - May require TREATMENT (not prophylaxis)
      - Discuss/refer to hepatologist urgently

- sAg +ve
  - undetectable DNA normal LFTs
    - Commence lamivudine 100mg od (dose reduce if renal impairment)
      - Refer to hepatologist immediately

Detectable DNA Abnormal LFTs

- cAb +ve only undetectable DNA normal LFTs
  - Monitor LFTs. If become abnormal, check DNA and refer to hepatologist urgently

Screen in high risk groups sAg +ve +/or cAb +ve
- Check HBV DNA + LFTs

Other immunosuppressive regimes eg short course steroids, methotrexate, azathioprine therapies for IBD, CTDs, rheumatology etc

- sAg +ve, detectable DNA or abnormal LFTs refer to hepatologist prior to treatment (normal work-up required).
  - At risk of reactivation so monitor, but risk lower and not quantified, prophylaxis not supported.

Hepatologist to advise as appropriate (see Hep B guidelines). Urgent assessment and advice so as not to delay cancer treatment

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Guideline Provenance
Guidance first written by Dr Rebecca Jones and Dr Mark Aldersley initially for WYHN following network meeting in 2008. This was in response to requests from network members. Kept as joint network/SJUH guidance. Reviewed at meeting 2009. Adapted to WEYHN and then YHLN guidance with respective name changes in 2010 and 2012. Review date October 2013.