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PLASMA-DERIVED MEDICINAL PRODUCTS: POSITION PAPER ON ALT TESTING

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Introduction

The ALT test measures the level of alanine aminotransferase as an indicator of liver cell damage. As such it is a surrogate test for the presence of viruses that cause liver cell damage. ALT screening of donor blood was introduced in several countries (e.g. in Germany in the mid 1960s, France in the mid 1980s) in order to prevent transmission of hepatitis to recipients of plasma derivatives. After introduction of specific testing of hepatitis B virus the ALT test was intended to detect what was then known as non-A, non-B hepatitis (now known to be primarily due to infection with hepatitis C virus (HCV)). After introduction of a specific test for hepatitis C antibodies in 1991, the usefulness of the ALT test can be reconsidered. At present the test is required in the EU in Austria, Belgium, France, Germany, Italy and Portugal while the other EU member states do not require ALT testing[1] (*Commission Staff Working Paper, 1997)*.

Present value of ALT testing

Hepatitis C virus

There is general agreement that the test no longer adds to blood safety as far as hepatitis C is concerned (*Blajchman et al. 1995; Busch et al. 1995; NIH, 1995)*. This was also confirmed by a meta-analysis of prospective clinical European studies on ALT testing for the prevention of non-A, non-B hepatitis following introduction of anti-HCV testing (*van der Poel, 1995*) which showed no beneficial effect for ALT screening after introduction of anti-HCV screening. The development of more sensitive tests for anti-HCV and, in the case of plasma-derived products, the requirement of nucleic acid amplification technology (NAT) testing for HCV in plasma pools as from July 1999 renders ALT testing for HCV even further redundant.

Hepatitis B

ALT testing might have benefit in detecting HBsAg mutants (*Jongerius et al, 1998; Hsu et al, 1997*) that escape the routine screen for HBsAg. However, if HBsAg mutants were considered to present a safety risk for plasma-derived products a more specific test such as NAT testing for hepatitis B virus (HBV) would be appropriate. In this context it must be remembered that the manufacturing processes for all plasma-derived products should include effective inactivation/removal steps for enveloped viruses such as hepatitis B.

Hepatitis A

There are currently no requirements for the screening of donations or plasma pools for hepatitis A virus (HAV). It has been argued that ALT testing will screen out donors with hepatitis A infections. However, an investigation on HAV transmissions caused by factor VIII concentrates several years ago led to the conclusion that the donors involved did not have elevated ALT levels at the time of donation. Also the fact that HAV transmissions by plasma products have happened where plasma is sourced from ALT-testing and non-ALT-testing countries, confirms that the ALT test is not a reliable screening test as far as HAV infection is concerned. This is not unexpected since the brief period of viremia seen with hepatitis A largely precedes the rise in ALT (*NIH, 1995*). Manufacturers have introduced, or are introducing into their manufacturing processes for coagulation factors, effective steps for the inactivation/removal of non-enveloped viruses such as hepatitis A. If it was considered

[1] Finland and Ireland have confirmed to the BWP that ALT testing is not a national requirement.

necessary to also introduce a screening test for hepatitis A, a more specific test is needed (e.g. NAT).

Parvovirus B19

Human parvovirus B19 may be associated with acute hepatitis with elevated ALT (*Yoto et al., 1996; Hillingsø et al., 1998; Naides et al., 1996; Tsuda, 1993*). Parvovirus B19 is frequently transmitted through blood products and the virus inactivating methods have shown to poorly prevent transmission (*Mauser et al. 1998; Rollag et al., 1998, Santagostino et al., 1997*). ALT testing will only detect parvovirus B19 infections that have associated hepatitis. Therefore, the test will not prevent parvovirus B19 entering plasma pools and potential transmission by coagulation factor concentrates. This is illustrated by a study where B19 seroconversion (IgM) and B19 viremia were observed within 2 weeks of the first concentrate infusion in 8 of 15 susceptible patients treated with Factor VIII and IX from ALT screened donations (*Santagostino et al., 1997*).

Other viruses

Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) are examples of viruses which might be detected by ALT testing. However, these viruses are not transmitted via plasma-derived products.

Hepatitis G virus (HGV) or GB virus C (GBV-C) has not been found to be associated with significant hepatic disease or symptoms and no other disease association has been identified. A recent study (*Blair et al., 1998*) on HGV/GBV-C in Scottish blood donors revealed no elevated ALT levels in infected donors.

It is still unclear whether the recently identified TT virus (TTV) is associated with disease. Recent data suggest that TTV, similar to HGV/GBV-C may be a human virus without clear disease association. Although some cases of transient infection associated with fulminant hepatitis have been reported (*Okamoto et al., 1998*), recent data suggest that there is also no clear correlation between TTV DNA levels and ALT levels (*Simmonds et al., 1998; Naoumov et al., 1998; Cossart 1998*).

ALT testing might be useful in screening out as yet unidentified viruses causing liver damage but this is inherently speculative.

Lack of specificity

ALT levels can rise because of various factors such as age, gender, obesity and alcohol use that are not necessarily related to infectious diseases. As a consequence, donors are deferred and donations are rejected where no transmissible infectious disease exists. Also, non-specificity of ALT may mean that donors could have a transmissible infectious hepatitis with an elevated ALT below the cut-off value.

Recommendations/requirements with respect to ALT testing

The Adare Colloquium on Blood Safety and Self-sufficiency held in 1996, under the auspices of the Irish presidency of the EU and with the support of the European Commission, concluded that ALT screening had become redundant (*Colloquium on Blood Safety and Self-Sufficiency, 1996)*. The NIH Consensus Panel on Infectious Disease Testing for Blood Transfusions held in January 1995 made a similar recommendation i.e. that ALT testing of volunteer blood donors is no longer scientifically valid and therefore could be discontinued (*NIH, 1995*), which was confirmed by the FDA's Blood Product Advisory Committee in March 1995 (*BPAC, 1995*).

There is no core requirement for ALT testing of plasma for production of plasma derivatives in any European Directive, guideline or Pharmacopoeia. In most regulations there is however a statement that competent authorities may require additional screening tests (*Ph.Eur. monograph on human plasma for fractionation, 1998; Council of the European Union Recommendation, 1998*).

On request of the Ph.Eur. Commission, expert group 6B on blood products carried out a review of the current status of ALT testing as applied in the screening of donors of plasma for fractionation during its meeting in October 1998. It was concluded that there is at present an irreconcilable split on ALT testing among Member States.

The CPMP guideline on plasma-derived medicinal products states that in particular each donation must be tested for HBsAg, antibody to HIV1 and HIV2, and antibody to HCV (*CPMP Note for Guidance, 1998*).

Lack of harmonisation on ALT and marketing authorisation of plasma derivatives in the EU

Lack of harmonisation on ALT testing was already identified in 1994 (*Ad Hoc Working Party on Biotechnology/Pharmacy, position paper, 1994*). Due to this lack of harmonisation on ALT testing, barriers for marketing in the EU of plasma derivatives derived from non-ALT tested plasma remain. An example of this barrier has been encountered with one of the first applications for a plasma derivative in the centralised procedure. Since in this case the plasma has been derived from European donations, the principle of self-sufficiency within the European Union also has a bearing. This example clearly illustrates the urgent need for harmonisation on ALT testing for plasma derivatives among EU Member States.

CONCLUSION

Measures taken to prevent infection by the use of plasma-derived products include selection of donors, screening of individual donations and starting materials for markers of infection with known viruses and validation of the production process for the inactivation or removal of viruses. The incorporation into manufacturing processes of effective steps for the inactivation/removal of a wide range of viruses of diverse physico-chemical characteristics provides the best safeguard against transmission of as yet unidentified viruses. Once the causative agent has been identified, sensitive and specific screening tests can be developed.

There is no clear benefit from ALT testing for identified viruses but a possible role for screening out as yet unidentified viruses causing liver damage cannot be excluded. However, the test is non-specific and excludes donations that do not pose any safety risk.

There is no core requirement in any EU legislation for ALT testing of plasma for production of plasma derivatives. The current lack of harmonisation among Member States on ALT as a requirement for testing of donor blood for production of plasma derivatives obstructs Marketing Authorisations in the European procedures of plasma derivatives produced from plasma collected without ALT testing.

RECOMMENDATION

Major improvements in donor selection, specific screening test methods and manufacturing processes have been achieved during the past years. There is no evidence that ALT testing provides any significant increase of safety for plasma-derived medicinal products.

Thus, with the current state of the art of manufacture and control of plasma-derived medicinal products, as defined in the note for guidance CPMP/BWP/269/95, rev.2, there is no scientific basis for objecting to the use of plasma for fractionation collected without ALT testing.

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