Comparison Of Clot Lysis Activity and Biochemical Properties Of Originator Tenecteplase (Metalyse®) With Those Of An Alleged Biosimilar (Elaxim®)

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The recombinant tissue plasminogen activator tenecteplase (TNK) is an important treatment modality of acute myocardial infarction. Following introduction of originator TNK (brand names Metalyse® and TNKase®), a ‘biosimilar’ TNK became available for commercial use in India and some other Asian countries under the brand name Elaxim® in the absence of Indian biosimilar guidelines which came into force from September 15, 2012. Based on a report of biochemical and functional differences between Elaxim and Metalyse (1), we have systematically compared them in a range of routine quality testing assays.

A representative commercial batch of Metalyse (#22579) was compared to two commercial batches of Elaxim (#140903 and #140904E04 obtained from an Indian pharmacy) using highly validated high precision methods and standard operating procedures which are applied to the routine quality testing of TNK batches within Boehringer Ingelheim prior to release for clinical use. The various parameters have been associated with biological activity, and all reported differences between Metalyse and Elaxim fall way outside the confidence limits of the respective assay; hence, our data are typically based on single experiments and results are reported accordingly.

Elaxim had the expected TNK amino acid sequence. However, clot lysis (determined by an automated ACL TOP® hemostasis testing system) relative to reference standard was 97% for Metalyse as compared to 77% and 76% for two Elaxim batches. The relative abundance of the two-chain form of TNK (determined by high-performance size-exclusion chromatography) was 31% for Metalyse as compared to 17% and 13% for Elaxim. In vitro conversion to the two-chain form was slower for Elaxim, and even fully converted two-chain form exhibited less clot lysis activity (117% and 103% for Elaxim vs. 128% for Metalyse). This was linked to differences in glycosylation pattern (determined by mass spectrometry) with Elaxim exhibiting less bi- and more tetra-antennary glycosylation (bi-antennary 44% and 48% for Elaxim vs. 58% for Metalyse, tetra-antennary 28% and 27% for Elaxim vs. 17% for Metalyse). Accordingly sialylation was higher for Elaxim compared to Metalyse (determined by mass spectrometry), leading to charge heterogeneity (determined by isoelectric focusing). Regarding purity, Elaxim contained more TNK aggregates (2.9% and 2.9% for Elaxim vs. 1.0% for Metalyse in high performance size exclusion chromatography) and, in contrast to Metalyse, considerable amounts of Chinese hamster ovary cell protein (6590 U and 6990 U for Elaxim vs. < 15 U for Metalyse; determined by ELISA with polyclonal antibody against Chinese hamster ovary cell protein). High molecular weight impurities absent in Metalyse were seen in Elaxim in
gel electrophoresis with silver staining detection.

Taken together these data demonstrate that Metalyse and Elaxim differ considerably in clot lysis activity and biochemical properties. They question whether Elaxim indeed can be considered a ‘biosimilar’ of Metalyse, i.e. whether and to which extent the clinical efficacy and safety properties of Metalyse can be extrapolated to Elaxim.

(1) Jiang H et al, Anal Chem 82: 6154, 2010