P0400
Paper Poster Session
Viral pathogenesis and treatment targets

Genetic variability of UL5 helicase gene in clinical herpes simplex virus type 1

Emilie Frobert[1], Morgane Linas[1], Bruno Lina[2], Florence Morfin*[1]

[1]*Hospices Civils de Lyon, Laboratoire de Virologie, Lyon Cedex 04, France*

[2]*Hospices Civils de Lyon, Institut des Agents Infectieux (Iai) de Lyon - Centre de Biologie Et de Pathologie Nord, Laboratoire de Virologie, Lyon Cedex 04, France*

Background: Resistance of herpes simplex viruses (HSV) to conventional antiviral drugs acyclovir (ACV) and foscarnet (FOS) are an increasing concern in immunocompromised patients and particularly bone marrow transplant patients. Research in antiviral drugs leads to the emergence of new therapeutic classes, as inhibitors of the helicase-primase complex (HPI), pritelivir or amenamevir (Burrel et al., 2014; Tyring et al., 2012). These new molecules represent potential treatment option for herpes infections even for combination therapy due to synergistic effect when used with ACV (reviewed in James and Prichard, 2014). Before these treatments would be currently used, it is important to explore the genetic variability of *UL5* helicase gene.

Material/methods: Sequence analysis of the full-length *UL5* encoding HSV1 helicase gene from 32 ACV resistant clinical isolates was performed. From these ACV resistant strains, two were also cross resistant to FOS and one was an ACV / FOS and cidofovir (CDV) resistant strain. This last multi-resistant strain could be detected over a 3 months period and 5 strains were sequenced. Nucleotide sequences were compared with reference strains KOS HSV1 (GenBank accession number JQ673480.1, sequence from 12432 nucleotides to 15080) using SeqmanII software (DNAStar Inc.).

Results: *UL5* gene sequencing revealed 17 amino acid substitutions never reported before: D11H, L49I, L53R, L138V, S173L, A196T, A280T, V347I, N380S, S481N, A575V, V594A, V600A, M601I, A602T, A687T and T734A. Strains harboured at least 3 amino acid substitutions and up to 9 substitutions, with an average almost up to 5 substitutions per strain. HSV1 UL5presented a substitution frequency of 0.6 per 100 amino acids whereas UL23 and UL30 have been previously reported with rates of 1.6 and 0.4, respectively (Burrel et al, 2010, AAC). These data additionned with data already published revealed a variation of the total codon at 4%, whereas UL23 and UL30 were at 56% and 18%, respectively (personal data). The ACV/FOS/CDV multi-resistant strains detected from the same patient over a three months period showed that all sequences were identical.

Conclusions: These results provide new data on the variability of *UL5* helicase gene for HSV1, with the description of 17 new amino acid substitutions. Moreover, *UL5* helicase gene seems to present a significant variability even if not as high as *UL23*, probably related to their respective role during viral replication. The variation of the total codon has to be confirmed by sequencing more strains as it could be underestimated. As HPI appeared to be effective and safe for treatment of herpes infections (Tyring et al., 2012) and as these molecules could also be an option for treatment of resistant HSV strains to conventional antivirals (Himaki et al., 2012, AR), extented genotypic characterization is required to better detect resistance mutations that could alter HPI efficacity.