RELATIONSHIP BETWEEN 3'VDR HAPLOTYPES AND ACQUIRED RESISTANCE TO CLODRONATE TREATMENT IN PATIENTS WITH PAGET'S DISEASE OF BONE

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The $1,25(OH)_2D_3$/vitamin D receptor (VDR) system plays a key role in the pathogenesis of metabolic bone diseases, including Paget's bone disease (PDB). In these diseases, VDR allelic variants significantly influence the effectiveness of antiresorptive treatments. This retrospective case-control study was performed to evaluate the pharmacological response to clodronate treatment according to Bsm1, Taq1 and Fok1 VDR polymorphisms in 84 (M:F 48:36; mean age 60.2±9.1 years) patients with poliostotic PDB from Campania, Southern Italy.

All patients were treated from diagnosis for several cycles with intravenous clodronate infusion (1500 mg/cycle). The acquired resistance to clodronate treatment was defined as the failure of the total alkaline phosphatase serum levels to be suppressed to at least 50% of the patient's previous highest levels during a subsequent treatment course with the same compound (clodronate), which produced a >50% response after the first exposure. Considering the linkage disequilibrium between BsmI and TaqI VDR sites, PDB patients were classified as homozigous (BBtt and bbTT) or heterozygous in relation to BsmI-TaqI cluster.

The acquired resistance to clodronate occurs in 31 PDB patients (36.9%, M:F 17:14; mean age 58.2±8.9 years; i.e. resistant). The prevalence of bbTT haplotypes in PDB resistant patients is higher compared to those observed in PDB patients without clodronate acquired resistance (i.e. responders) (F 8.737; p 0.043). The relative risk to develop acquired resistance to clodronate treatment in homozigous bbTT PDB patients is 7.00 (95% C.I. 1.57-31.18). Additional analysis of FokI alleles was not more informative. No significant differences in clinical characteristics at diagnosis, time of observation, treatment courses and total dose of clodronate administration were found among resistant and responder PDB patients.

Our results confirm that the different VDR genetic variants significantly influence the action mechanism of bisphosphonate and suggest a link between 3'VDR allelic variants and the occurrence of acquired resistance to clodronate treatment in patients with poliostotic PDB.