SLOVENIAN NATIONAL DATA FOR INHIBITOR APPEARANCE IN HAEMOPHILIA A (HA) PATIENTS

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Introduction and objectives:

Inhibitor formation is now the major complication of haemophilia treatment. We wanted to identify the incidence of inhibitor formation in Slovenian haemophilia patient and treatment outcome.

Materials and methods:

We analyzed medical documentation of 219 HA patients (98 severe HA) in the period between 1977 and 2013. Inhibitors developed in 12 severe (12 %) and 3 mild HA patients, among them only 1 low responder.

Results:

Genetic analysis in 12 severe HA patients revealed 4 intron 22 inversion, 2 nonsense mutation, 1 splice site mutation, 3 small deletion (all from the same family), 1 missense mutation, and 1 small insertion. Five of these patients died: two due to bleeding, one due to traffic accident after successful high dose immune induction therapy (ITI), and two due to Hurler mucopolisacharidosis and Duchene muscular dystrophy, respectively. In 7 severe HA patients ITI was successfully done: 3 with low dose (30 IU/kg FVIII every other day) and 4 with high dose (100 to 200 IU once to twice daily). In 2 of them inhibitors developed after more than 200 exposure days, in both after intensive FVIII exposure with continuous infusion (CI). One of them, was HIV and HCV infected and received treatment for surgery of inflamed haematoma. After successful ITI, CI was used on 3 occasions additionally, without inhibitor reappearance. In one patient eradication of inhibitors was achieved by high dose ITI after 15 years of inhibitors appearance. One patient was a newborn (a relative of HIV patient) with intracranial bleeding after normal vaginal delivery who developed inhibitors after 16 days of CI. ITI at the age of three years led to inhibitor eradication in 5 months. In one severe adult patient inhibitors are still present. In three HA mild patients with missense mutations (1high risk Arg593Cys mutation, 2 brothers with Arg2307GIn mutation) inhibitors developed after intensive exposure with bolus and CI, respectively. In a patient with risk mutation longstanding immune tolerance was achieved by four doses of rituximab, whereas both brothers died due to bleeding.

Conclusions:

Despite, the high cost is a major disadvantage of ITI, if successful, it results in improved clinical outcomes and is cost saving over the course of a lifetime. Low dosage ITI is successful but more time is needed to eradicate inhibitors than with high-dose ITI, which has additional advantage of less or no bleedings during its course. Patients with mild HA and inhibitors may experience severe bleedings similar to those in acquired haemophila and maybe they need different ITI therapeutic approach.

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