INTRODUCTION

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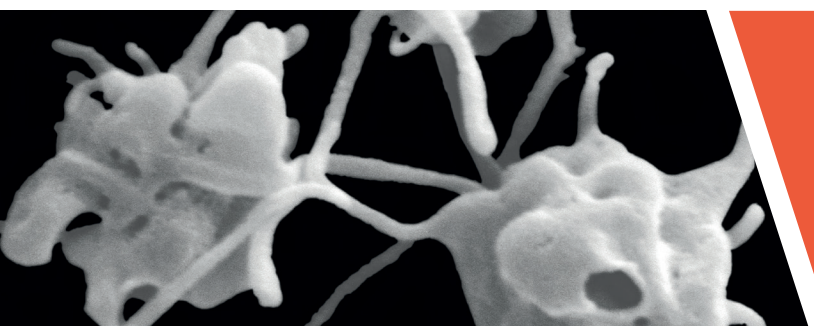
Heparin-induced Thrombocytopenia (HIT) remains a rare but severe and life-threatening complication of heparin therapy, presenting a higher incidence with Unfractionated (UFH) Heparin, than with Low Molecular Weight Heparin (LMWH) treatments. Risk to develop HIT is increased in some clinical situations, and with heparin exposure duration. This complication tends to occur more often in orthopedic patients, although the highest rate of antibody development is observed in Extra-Corporeal Circulation (ECC), Cardio Pulmonary Bypass (CPB) and ExtraCorporeal Membrane Oxygenation (ECMO), or in hemodialysis patients. However, recent big data analysis indicates a different incidence of HIT than previously reported, in the various clinical contexts where heparin is used. This incidence is reported lower in orthopedic patients, and the highest one is in ECC. Development of heparin dependent antibodies means the presence of an immune response, heparin dependent, mediated by Platelet Factor 4 (PF4), however most of the generated antibodies remain asymptomatic. These antibodies can be of the IgG, IgM or IgA isotype. They are targeted mainly to Heparin-Platelet Factor complexes (HPF4) in typical HIT, but some disease variants are associated with heparin dependent antibodies targeted to other antigens than PF4 (Interleukin-8/IL8, Neutrophil-Activating Peptide 2/NAP2, or Protamine Sulfate), as this has been reported. Symptomatic antibodies are mainly of the IgG isotype, although many of them can remain asymptomatic. Factors which contribute to render antibodies pathogenic are not fully understood, but antibodies with the highest affinity to HPF4 complexes or to PF4 are those with the highest capacity to activate platelets. Antibody bind to platelets through the antigen site (onto platelet bound HPF4 complexes), and through their IgG-Fc fragment to platelet FC-γ-RIIA receptors (CD32). This binding produces platelet activation and destruction, and thrombosis can develop in some cases. Heparin dependent antibodies are generally formed between 5 and 15 days from the onset of heparin therapy and they are usually of the IgG isotype. IgM or IgA antibodies can develop in many heparin treated patients but remain asymptomatic,



excepted in rare cases. The direct and fast development of anti-HPF4 antibodies of the IgG isotype in symptomatic patients (but never previously exposed to heparin) suggests a former immune stimulation with PF4 complexed with glyco-amino-glycans (polyanions), this protein exposing then an altered structure. The HIT immune response, which develops during heparin therapy, could then be secondary (anamnestic) to a former immune stimulation. The primary stimulation could be consecutive to an infectious episode, PF4 binding to bacterial polysaccharides, and inducing a self-response. The higher incidence of HIT in patients with former periodontitis or gum diseases supports this hypothesis.

Laboratory diagnosis of HIT is of major importance as this complication becomes rapidly severe and life threatening and can provoke limb amputation in some patients. The first action in presence of HIT suspicion is to withdraw heparin and to switch to an alternative anticoagulant. However, if HIT is excluded, patients can benefit again from the high therapeutic and antithrombotic efficacy of this drug, which remains superior to all the substitutive anticoagulant treatments. HIT is suspected in presence of a platelet count drop > 50% (eventually 30%) on 2 successive counts, or a platelet count < 100 G/L, and in presence of a significant clinical probability (4Ts score). This clinical evaluation is addressed later in this report. In addition to the clinical probability, laboratory testing of patients' plasma is required for establishing the HIT diagnosis. Laboratory investigation involves the immunological measurement of heparin dependent antibodies, and, when positive, confirmation of diagnosis with a functional assay is required to demonstrate platelet activation. The confirmation test is performed at a low and high heparin concentration, and platelet activation occurs only at low heparin concentration, but not at high. In any case, if the immuno-assay is negative, HIT can be excluded with a high probability, and heparin can be continued (if clinical examination favors this decision). Conversely, higher is the IgG antibody concentration measured with the immunoassay, and higher is the probability of HIT.

Nevertheless, immunoassays lack of "clinical specificity", as many antibodies, although IgG, remain asymptomatic.