Monitoring of P2Y12 receptor antagonists

PLT VASP/P2Y12
Ref. # 7014

Clinical applications:
Monitoring of specific platelet ADP receptor (P2Y12) antagonists (Thienopyridines and analogues)

Pharmaceutical applications:
New drug discovery and validation of new P2Y12 antagonists

Technology:
Flow cytometry

Sample:
Citrated whole blood

Preanalytical feature:
48H sample stability

Biological evaluations:

In Europe, For In Vitro Diagnostic Use
Monitoring of P2Y12 receptor antagonists:

**Background:**
ADP is one of the most important mediators of haemostasis. It leads to platelet activation through two G-protein coupled receptors, P2Y1 and P2Y12. The P2Y1 receptor is responsible for the initiation of ADP-induced aggregation while the P2Y12 receptor mediates completion and amplification of the aggregation response.

**Monitoring of Thienopyridine:**
Clopidogrel is an antiplatelet drug which inhibits the P2Y12 receptor. Alone or in association with Aspirine, this drug has proved efficacy in the prevention of atherothrombotic complications. However, several studies have recently described inter-individual variability and resistance to Clopidogrel:

1. **GURBEL P.A. et al. (2003)**
   *Circulation* 107 : 2908-2913
2. **MULLER I. et al. (2003)**
   *Thromb Haemost.* 89 : 783-787
3. **SEREBRUANY V.L et al. (2005)**
   J AM Coll Cardiol 45 : 246-251

**Test interpretation:**
A platelet reactivity index (PRI) is calculated using corrected mean fluorescence intensities (MFIc) in the presence of PGE1 alone, MFIc (PGE1), or PGE1 and ADP simultaneously, MFIc (PGE1 + ADP), according to the following calculation:

\[
PRI = \left( \frac{MFIc (PGE1) - MFIc (PGE1 + ADP)}{MFIc (PGE1)} \right) \times 100
\]

**Diagnostic test:**
VASP (Vasodilator Stimulated Phosphoprotein) is an intracellular platelet protein which is non phosphorylated at basal state. VASP phosphorylation is regulated by the cAMP (cyclic Adenosine Monophosphate) cascade. PGE1 (Prostaglandin E1) activates this cascade whereas it is inhibited by ADP (Adenosine Diphosphate) through P2Y12 receptor. In the test conditions, VASP phosphorylation correlates with the P2Y12 receptor inhibition, whereas its non-phosphorylation state correlates with the active form of P2Y12 receptor.

**HOW?**

1. **Determine basal PRI range**
2. **Determine PRI**
3. **Repeat PRI VASP/2Y12**
4. **Is PRI in basal PRI range?**
   - **YES**
     - **Determine PRI**
     - **PRI still included in basal PRI range:** **Bad responder**
   - **NO**
     - **Is PRI in basal PRI range?**
     - **YES**
     - **Determine PRI**
     - **PRI still included in basal PRI range:** **Bad responder**

**WHO?**

1. **Group of patients relevant of the disease of interest and not receiving the P2Y12 antagonist to evaluate**
2. **Patient to be tested before treatment (PRI0)**
3. **Patient to be tested, treated with the P2Y12 antagonist of interest during a period of time T (PRI), according to the pharmacodynamic properties of the treatment.**

**VASP/P2Y12** allows to evaluate the efficacy of Thienopyridines ex vivo measuring the persistence of VASP phosphorylation induced by PGE1 even with the simultaneous addition of ADP. VASP/P2Y12 could also be used to evaluate in vitro effects of P2Y12 receptor antagonists.

**Conclusion:**

- The PRI is a valid tool for evaluating the response to P2Y12 antagonists.
- Individual variability and resistance to Clopidogrel should be considered.

**References:**

- **ALEIL B. et al.; (2005)**