IATDMCT CONSENSUS DOCUMENT ON TDM OF EVEROLIMUS

Maria Shipkova,
Central Institute of Clinical Chemistry and Laboratory Medicine, Klinikum-Stuttgart
Germany

Scope of the lecture:
The lecture will provide an overview of the content of the Consensus Document on Therapeutic Drug Monitoring of Everolimus, developed by the Immunosuppressive Drugs Scientific Committee of IATDMCT

Learning objectives:
1. The process of development and the outline of the Consensus Document will be explained
2. The certain criteria for TDM of everolimus and the recommendations on why and when TDM of everolimus is needed as well as how to perform it will be emphasized
3. The evidence available regarding the potency of some pharmacogenetic and pharmacodynamic biomarkers as tools to complement classic pharmacokinetics based TDM will be discussed

Extended abstract:

IATDMCT CONSENSUS DOCUMENT ON TDM OF EVEROLIMUS

The Immunosuppressive Drugs Scientific Committee of IATDMCT is dedicated to optimizing therapy with immunosuppressive drugs. One of the aims of the Committee is to provide evidence-based recommendations for Therapeutic Drug Monitoring (TDM) for these drugs. Over the last years consensus documents on TDM of cyclosporine A, tacrolimus, sirolimus and mycophenolic acid have been developed as well as published and during the Committee meeting at the 13th international congress of the IATDMCT in Salt Lake City (2013) the members decided to initiate the work on such a document on the TDM of evarolimus (EVL).

EVL entered clinical development first as a part of therapeutic protocols for the prevention of organ transplant rejection and, later, as an approved agent for the treatment of a variety of non-transplant applications including cancers and tuberous sclerosis complex. Similar to other immunosuppressive drugs, a narrow therapeutic window, a rather high intra- and inter-individual pharmacokinetic variability, as well as established drug exposure-response relationships have been demonstrated for EVL.

The EVL Consensus Document was developed between 2013 and 2015 drawing on the expertise of clinical pharmacologists, clinicians, pharmacists, and analysts involved in

therapeutic drug monitoring of mTOR inhibitors. For the purposes of the project three working groups responsible for different aspects of the issue were established. These groups consisted not only of members of the Immunosuppressive Drugs Scientific Committee but also of external experts, who were invited to join the groups in order to ensure the highest possible level of quality. Members of the first group, that focused on the clinical pharmacology of EVL, were Pierre Marquet (France), Eliane Billaud (France), Olga Millán (Spain), Mercè Brunet (Spain), Eberhard Wieland (Germany) and Alexander Vinks (USA). The work of the second group covered the evidence available for TDM of EVL in different clinical situations. Its members were Teun van Gelder and Dennis Hesselink (The Netherlands), Michael Oellerich (Germany), Satohiro Masuda (Japan), Loralie Langman (USA), Ray Morris (Australia), Klemens Budde (Germany), Markus Barten (Germany), and Paolo De Simone (Italy). Maria Shipkova (Germany), David Holt (United Kingdom), Christoph Seger (Austria), Pawel Kunicki (Poland), Pierre Wallemacq (Belgium) and Carol Thompson (USA) took care of the tasks for the third group, the analytical aspects of the quantification of EVL; Maria Shipkova and David Holt coordinated the activities.

The final version that provides a profound overview on all aspects related to TDM of EVL (including drug characteristics, specific clinical situations, and methodological issues) was published in 2016 as an open access article in the IATDMCT Journal "*Therapeutic Drug Monitoring*". The aim of the document is to improve both standards of practice and patient care. It is mainly directed at all professionals who are involved in the management of transplant patients (including pathologists, toxicologists, and transplant clinicians) but includes also information of interest for those working with EVL for non-transplant applications.

The outline of the Consensus Document includes nine parts as shown in the table:

I. **Brief introduction**
II. **EVL formulations**
III. **Chemistry and mechanism of action**
IV. **General safety**
V. **Pharmacokinetic monitoring**
    1. Pharmacokinetics of EVL
    2. Drug-drug and drug-food interactions
    3. Compatibility of EVL characteristics with the prerequisites for TDM and TDM strategy
VI. **Evidence-based TDM for EVL in specific clinical situations**
    1. Kidney-, Liver-, Heart- and Lung transplantation
    2. Oncology
    3. Tuberous sclerosis complex
    4. Pulmonary arterial hypertension
VII. **Pharmacogenetic monitoring**
VIII. **Pharmacodynamic monitoring**
IX. **Measurement of EVL concentrations**
    1. Sample stability
    2. Analytical methods
    3. Analytical requirements
    4. Method calibration and proficiency testing

After reviewing the scientific background and the evidence generated, each section of the Consensus Document ends with practical recommendations supporting an optimal implementation of TDM in clinical practice. Rather than providing guidance on the indications to select an EVL comprising therapy in a particular clinical situation the Consensus Document focuses on the best practice for monitoring this therapy to allow its individualization. Unmet needs and fields of limited evidence that have to be addressed in the future are discussed.