Biomarkers in Solid Organ Transplantation: Prospects and Challenges

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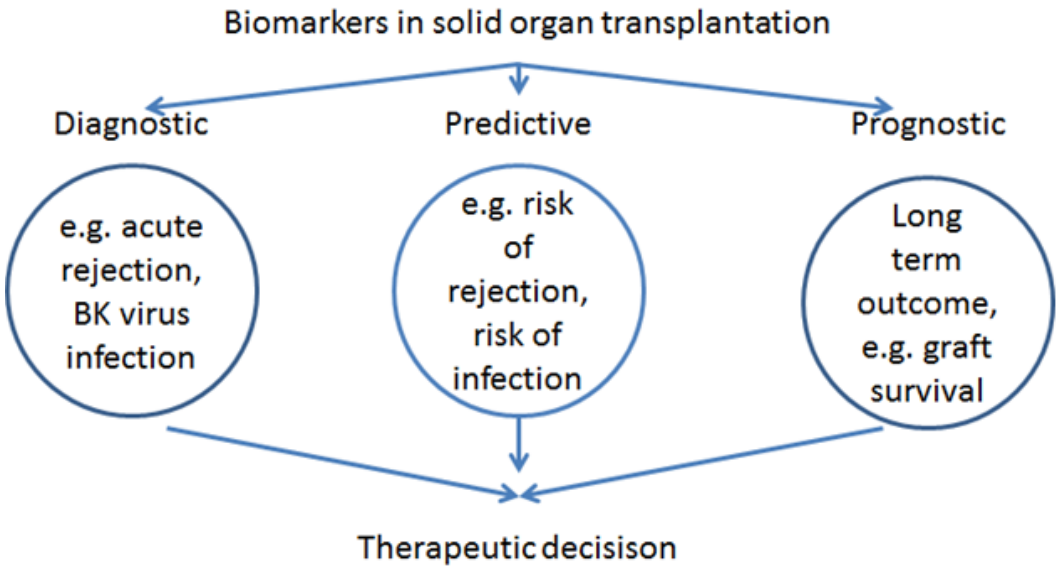
Scope of the lecture:
The scope of the lecture will be to show prospects for biomarkers to complement therapeutic drug monitoring of immunosuppressants in solid organ transplantation but also to point to the pitfalls and challenges in the analytical and clinical validation of biomarker assays. An overview of promising minimally invasive candidate biomarkers will be given.

Learning objectives:
1. Why there is a need for biomarkers to better individualize immunosuppression in solid organ transplantation?
2. To distinguish diagnostic, predictive and prognostic biomarkers.
3. Principles of analytical and diagnostic validation of biomarkers.

Extended abstract:

Individualized immunosuppression is the ultimate goal to improve long term graft and patient survival. Recent progress in medical care of transplant patients has resulted in very low acute rejection rates early after transplantation and in an increasing number of patients who live for extended time periods with a donor organ. However, the interplay between immunogenicity of the donor organ, the immune system of the graft recipient and the immnunosupressive therapy is complex and requires fines tuning. After transplantation patients are clinically evaluated on a regular basis including laboratory tests, sometimes receive invasive organ biopsies to monitor possible graft damage, and the dose of calcineurin and mTOR inhbitors is adjusted based on therapeutic drug monitoring. These currently practiced procedures are however far from being optimal. To improve this situation there is worldwide searches for biomarkers which help to better diagnose organ damage, to predict clinical complications, and which are prognostic for long term outcome. Ultimately therapeutic decision should be individualized based on this information.



It is obvious that these expectations cannot be met by one single biomarker but much more likely by a combination of appropriate candidates. It can be expected that the suitable combination depends on the transplanted organ and endpoint of interest. In addition, before the utility of a biomarker panel can be evaluated, every single biomarker has to prove its analytical performance as well as its diagnostic specificity and sensitivity.

Major challenges in biomarker development are therefore the analytical reliability and reproducibility of assays to perform biomarker measurements and appropriate clinical trials to establish their utility. Because the prevalence of clinical events is sometimes rather low and the observation period is frequently long multicenter trials are required to recruit a sufficient number of patients and events. This further complicates the situation because pre-analytical and stability issues as well as comparability of biomarker test results between different laboratories come into play. To be suitable for the clinical purposes mentioned above biomarker assays must not be only robust and standardized but results must be also available for the clinician within a reasonable time frame for their implementation in therapeutic decisions. Before this becomes reality randomized prospective clinical outcome trials are needed.

Although there has been a wide variety of candidate biomarkers proposed in the literature partly based on sophisticated and promising omic and molecular biological technologies none of them has made its way into patient care so far. This is mainly due to the challenges addressed above.