

ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové

Training Workplace Department of Social and Clinical Pharmacy

Doctoral Degree Program Clinical and Social Pharmacy

Candidate Mgr. Barbora Košťálová

Supervisor doc. PharmDr. Josef Malý, Ph.D.

Advisor

Title of Doctoral Thesis Contextual analysis of medication adherence in patients after kidney transplantation

Introduction: Strict adherence to immunosuppressive medication (IS) is essential for organ transplant patients to minimize the risk of graft rejection. Growing number of randomized controlled trials (RCTs) shows the effectiveness of interventions to enhance medication adherence in transplantation, however, the real-world implementation is still a major challenge. The objective of the thesis was to analyze medication adherence in the context of selected clinical and behavioral aspects in Czech kidney transplant outpatients and to evaluate the range of information available in RCTs to support real-world implementation of adherence-enhancing interventions.

Methods: 1) The cross-sectional study was conducted between April and December 2019 in the Transplant clinic of the University Hospital Hradec Králové. All adult outpatients were approached during their scheduled visit at the clinic. Data was collected via patient-administered questionnaires and the review of medical documentation. Data analysis involved: a) prevalence of self-reported adherence to IS measured by the Czech translation of the international BAASIS© questionnaire; b) the comparison of different calculations of tacrolimus blood concentration's intra-patient variability using regression analysis modelling; c) evaluation of changes in adherence and beliefs about IS over the three-year period including patients who participated in the previous study at the clinic; d) investigation of relation between beliefs and de-novo malignancy or graft functioning using a generalized linear model; e) assessment of patients' awareness and level of photoprotection; f) evaluation of skin cancer incidence and related risk factors. 2) The systematic review included RCTs of interventions that targeted any phase of medication adherence in adult solid organ or allogeneic stem cell transplantation recipients and were published between January 2015 and November 2020. Relevant trial registries as well as traced references backward and citations forward were also identified. Implementation-relevant information was evaluated by adapted versions of Peters' criteria using a stoplight color-rating system.

Results: 1) All 410 patients enrolled in the clinic were included in the study. The questionnaire survey completed 361 (93%) out of 390 addressed patients. a) Non-adherence to IS according to BAASIS© was recorded in 137 (38% or 361) patients. The most frequent problem was the wrong timing of IS. b) Total of 243 (67%) patients were on tacrolimus-based immunosuppression. Self-reported non-adherence was predicted by higher coefficient of variability, even if time-weighted. A nonlinear relationship between tacrolimus dose and tacrolimus blood concentrations was observed, finding generally lower concentrations for patients admitting non-adherence. c) Longitudinal data on adherence and beliefs were available for 134 (37%) patients. Over time, their perceived treatment necessity beliefs of IS decreased, while concerns about taking them increased. d) Higher baseline treatment concerns were associated with non-adherence and with de-novo malignancy whereas higher baseline treatment necessity beliefs corresponded with better kidney functioning. Both results remained significant after adjusting for age. e) Out of 361 respondents, the bright phototype (I or II) was detected in approximately a quarter of patients without a diagnosis of skin cancer and in almost half of patients with this diagnosis. About a third of patients reported

moving in direct sunlight for more than 30 minutes almost every day. The use of sunscreens was reported by 239 (66%) patients, but almost a third did not answer this question. f) Posttransplant cancer was reported in 123 (30% of 410) patients. The most common were skin tumors. The risk factors for the occurrence of their occurrence were use of cyclosporine immediately after transplantation ($p < 0.05$), older age at the time of transplantation ($p < 0.001$) and longer time after transplantation. As in the general population, the patient's biological age also affected the incidence of skin tumors. 2) Screening of 17 004 titles/abstracts resulted in 23 eligible RCTs, including 2 339 patients ($n = 19-209$). All included studies were focused on the implementation phase of medication adherence. The best-reported criteria were feasibility study (43%), representative sample (17%) and conducted in a real-world-setting (17%). Least reported were study context (9%), implementation strategies (4%) and process evaluation (4%).

Conclusion: Non-adherence to IS is common in kidney transplant patients. For regular adherence monitoring, the clinicians may use the Czech translation of the BAASIS© questionnaire alone or in the combination with the coefficient of variability of tacrolimus concentration. Decreasing treatment necessity beliefs on one hand, and increasing treatment concerns on the other, should be considered in clinical practice. It is also necessary to emphasize other aspects of patients' attitudes toward pharmacotherapy, including interdisciplinary education of patients regarding regular photoprotection in order to minimize the risk of skin tumors. To implement medication adherence enhancing interventions, we do not have sufficient information in the literature. This hinders their translation to real-world transplant settings. Integrating implementation science principles early in the conceptualization of RCTs would fuel real-world-translation, reducing research waste.

Abbreviations: IS: immunosuppressive medication, RCTs: randomized-controlled trials.