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Original Investigation

The Consistency and Reporting of Quality-of-Life Outcomes in Trials of Immunosuppressive Agents in Kidney Transplantation: A Systematic Review and Meta-analysis

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Background: Shared decision making regarding immunosuppression in kidney transplantation requires an understanding of effects on quality of life (QoL). Our aim was to review the frequency and reliability of QoL measures reported in randomized controlled trials of maintenance immunosuppression following kidney transplantation.

Study Design: Systematic literature review.

Setting & Population: Kidney transplant recipients enrolled in randomized trials of maintenance immunosuppression.

Selection Criteria for Studies: Systematic search of the Cochrane Kidney and Transplant register, CENTRAL, MEDLINE, EMBASE, PsycINFO, and CINAHL databases to January 2014 identifying maintenance immunosuppression trials. An EQUATOR Network–endorsed checklist was used to assess QoL reporting and effect sizes estimated.

Intervention: Maintenance immunosuppression (comparative studies, dose adjustment, and agent withdrawal).

Outcomes: Any quantitative patient-reported measure of physical, emotional, or social well-being.

Results: Of 2,272 reports, 41 (2%; involving 4,549 participants from 23 trials) included QoL outcomes using 22 instruments (8 generic, 2 disease specific, and 12 symptom specific). Reporting was incomplete for the majority with 1 (4%) addressing all 11 items of the checklist, 4 (17%) addressing clinical significance, and 15 (65%) reporting outcomes selectively. Almost all (n = 96 [95%]) effect size estimates for 101 QoL outcomes (18 trials; 3,919 participants) favored the interventions, with 37 (37%) statistically significant. In comparison, 30 (73%) clinical outcomes favored the intervention and 13 (31%) were significant.

Limitations: QoL outcomes are commonly secondary outcomes and may not be indexed or found using text word searches. Effect sizes were estimated from different QoL measures, populations, and interventions. The small number of trials limits the ability to identify statistically significant associations between effect size and study-/patient-related factors.

Conclusions: QoL is infrequently reported in immunosuppression trials in kidney transplantation, appears subject to major biases, and thus may be unreliable for decision making.

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INDEX WORDS: Kidney transplantation; quality of life (QoL); health-related quality of life; maintenance immunosuppression; end-stage renal disease (ESRD); post-transplant immunosuppression; immunosuppressive agent; side effects; adverse events; symptoms; patient-reported outcomes; patient-centered care; systematic review; randomized controlled trials.

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Reporting of quality-of-life (QoL) outcomes in clinical trials is necessary to inform patient-centered care, particularly when treatments have differing side effects and adverse outcomes that affect patient experience and well-being.[1] Although kidney transplantation is the treatment of choice for most patients with end-stage kidney disease, lifelong immunosuppression is required to maintain optimal transplant function. Immunosuppressive drugs have differing side-effect profiles, affect QoL, and increase recipients' susceptibility to serious adverse outcomes,

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including cancer, infection, cardiovascular disease, and diabetes.[2,3]

Systematic reviews of clinical trials in kidney transplantation have shown that reporting of clinical outcomes, particularly adverse events, is inconsistent and incomplete, which means that published estimates of the benefits of treatment effects may be unreliable.[4] Inherently, subjective outcomes such as patient-reported QoL are at higher risk of bias as a consequence of inadequate randomization, allocation concealment, and blinding than are objective clinical outcomes,[5,6] leading to overestimation of the effects of interventions. Also, the variability of conduct and reporting of QoL outcomes adds additional uncertainty to the interpretation of trial data.[7,8] Consequently, the extent and reliability of data to support a full evaluation of the benefits and harms associated with long-term management of posttransplantation immunosuppression is unknown. This is of particular concern given the recent focus on patient-centered care, patient-relevant outcomes, and shared decision making.[9-12]

The aim of this study is to evaluate the frequency and reliability of QoL outcomes from randomized controlled trials of immunosuppressive drugs in kidney transplantation. Knowledge of the extent to which patient-relevant outcomes have been addressed in clinical trials can inform ways to develop and optimize strategies for informed shared decision making in kidney transplantation.

METHODS

Study Overview

We conducted a systematic review based on standard methods and reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[13]

Inclusion Criteria

All randomized controlled trials of maintenance immunosuppression interventions following kidney transplantation were included. Broad inclusion criteria for interventions were used, including different immunosuppressive agents, withdrawal or substitution of an agent from multiple drug regimens, variation in doses or schedules, or interventions aimed at maximizing efficacy (eg, therapeutic monitoring). There was no restriction by language, drugs, age of recipient, or multiple organ transplants.

Literature Search

The Cochrane Kidney and Transplant Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched from inception to October 3, 2015. Medical Subject Headings (MeSH) and text words relevant to kidney transplantation and immunosuppression were used to identify randomized controlled trials of maintenance immunosuppression interventions and combined with MeSH headings and text words relating to QoL, adverse events, side effects, and symptoms (Table S1, available as online supplementary material). Titles and abstracts were reviewed to identify articles for full-text review. Because inclusion of QoL outcomes in a trial may not be clear from a title and abstract search, an additional 200 citations were selected at random for full-text review.

Outcome Measures

We collected data for QoL and clinical outcomes. A QoL outcome was broadly defined as any patient-reported outcome providing a quantitative measure of well-being; mental, social, or physical functioning; or distress, impairment, or personal impact. Clinical outcomes reported, such as mortality, transplant failure, acute rejection, kidney function, treatment failure, and hospitalization time, were collected. The QoL instruments were classified as generic if applicable to a broad range of patient groups, diseases, or interventions and as specific if they targeted a particular patient group, disease, intervention, or domain.[14] Instruments were further classified as being specific to a disease or patient group or specific to a symptom or group of symptoms.

Assessment of Risk of Bias

The risk of bias of included trials was assessed independently by authors M.H. and H.T.T. using the Cochrane tool.[15] The reliability of reporting of QoL outcomes was assessed using a 11-item checklist endorsed by the EQUATOR (Enhancing the Quality and Transparency of Health Research) Network.[16] The checklist included 4 domains: conceptual (hypothesis and rationale for instrument), measurement covering psychometric properties (validity, reliability, and responsiveness), validity for the population and adequacy of domains, methodology (method of administration, baseline reporting, timing, and strategy for handling missing data), and interpretation (clinical significance and completeness of reporting). Risk of bias was ranked as very low, low, moderate, or high for the trial and QoL reporting was based on the number of items addressed by the trials.

Data Synthesis and Analysis

We extracted data for QoL and clinical outcomes and calculated effect sizes as the standardized mean difference for continuous outcomes and risk ratio for dichotomous outcomes for all included trials for which sufficient data were provided or could be estimated. In cases in which there was inadequate data, authors were approached for missing data. Because QoL instruments may include multiple domains and single or multiple composite scores, all of which may be pertinent to patient experience, we calculated an effect size for each outcome reported. We used the QoL and clinical outcomes recorded at the latest time to calculate effect size. When more than one treatment arm was included, we compared each arm to the control. Effect sizes were calculated so that a standardized mean difference greater than zero and/or a risk ratio greater than 1 could be interpreted as favoring the intervention group relative to the control.

Preplanned subgroup analyses stratified by risk of bias (trial and QoL), trial size, trial duration, primary versus secondary outcomes, type of QoL instrument, time since transplantation, and incidence of acute rejection were used to assess sources of heterogeneity. Summary estimates of effect sizes were calculated using the inverse variance method. To account for the correlation from multiple trial outcomes, a study-level random effect was also included in the models. $P \leq 0.05$ was considered statistically significant. Calculations were undertaken using RevMan, version 5.2 (The Nordic Cochrane Centre, Cochrane Collaboration), and SAS, version 9.3 (SAS Institute Inc).

RESULTS

Literature Search

We identified 2,381 relevant citations, of which 1,566 did not address QoL outcomes. Full-text analysis excluded 109 reports because they were nonrandomized trials or did not include a relevant intervention. The 200