Improving Clinical Governance of Kidney Transplantation: Review of a Ruling and of the Clinical Governance Process in the United Kingdom

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ABSTRACT

The presentation of adverse events and negative outcomes is uncommon in scientific publications, particularly in a highly regulated and scrutinized practice such as solid organ transplantation.

A ruling of a regulatory body of the pharmaceutical industry in the United Kingdom generates several considerations, in particular, regarding the governance process of kidney transplantation, as the events reported in the ruling are linked with high rejection rates and negative patient outcomes.

This analysis offered a review of the current governance processes, while recognizing the relevant limitations of the system regulating kidney transplantation outcomes in the United Kingdom.

The article identified some of the potential interventions that may contribute to delivering an improved governance, harmonizing contemporary practice, modern health care system, and establishing scientific knowledge.

THE success of solid organ transplantation (SOT) over the last decades has been enabled by the consolidation of highly effective and tolerable immunosuppressive protocols.

In kidney transplantation (KT), a wealth of rigorously designed and successful trials have shaped our current clinical practice. In particular, the knowledge that we have acquired in the prophylaxis of acute rejection, translated into a globally reproducible reduction of biopsy-proven acute rejection (BPAR), has contributed over the years to a progressive and substantial improvement of patient survival (PS) and graft survival (GS) rates. The formulation and implementation of new immunosuppressive protocols continues to represent a crucial and highly sensitive part of SOT.

In the United Kingdom, dedicated regulatory bodies ensure patient safety and evidence-based practice in both the clinical and research spectrum of SOT, as well as in any other branch of medical practice.

The Prescription of Medicine Code of Practice Authority (PMCPA) covers an important role, as it is "the self-regulatory body which administers the Association of the British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry, independently of the ABPI" [1].

A ruling of the PMCPA [2] regarding the involvement of a pharmaceutical company with the adoption of a new immunosuppressive protocol for the recipients of a kidney transplant from a living donor (KTLD) has exposed some relevant limitations of the current quality measurements of the outcomes of KT services.

This analysis aimed to apply the content of the PMCPA ruling to considerations and reflections concerning the clinical governance of KT.

CASE AND RULING SUMMARY

The case related to the adoption of a new immunosuppressive protocol in a transplant unit of the UK. The protocol is described in Table 1. The PMCPA noted that the protocol described was not a research protocol; instead, it represented the standard prophylaxis for acute rejection prescribed to all of the suitable recipients of a KTLD in the anonymized transplant

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Table 1. Immunosuppression Protocol

Induction	Basiliximab
Maintenance	Once daily prolonged release tacrolimus Azathioprine Steroids rapid withdrawal (1 wk)

This protocol was prescribed to all recipients of a kidney transplant from a living donor considered at low or standard risk of rejection defined as: recipients of first kidney transplant, absence of donor specific antibodies, and with ≤3 human leucocyte antigens mismatch.

center (TxC). Also, such protocol was in place for almost 3 years before being discontinued [2].

The case summary indicated that the concerns presented to the attention of the PMCPA initiated with the observation of high rejection rates. Subsequently, further concerns were raised regarding potentially improper fundings, linked with the adoption of a specific immunosuppressant in the clinical protocol [2].

It is noted in the PMCPA ruling that an extraordinarily high rate of BPAR was observed among KTLD recipients who received the new immunosuppressive protocol [2].

After the review of the extensive documentation made available at the hearing, the PMCPA concluded that there was a strong link between the inclusion of an immunosuppressant in the new clinical protocol with a payment given in the form of a grant, by the same company to clinicians of the transplant unit [2], through the hospital charity.

The ruling of the PMCPA established that the pharmaceutical company was in breach of 3 clauses (Table 2). The PMCPA also reported that "the pharmaceutical company had accepted all the rulings of breaches" and undertakings were received; further sanctions against the pharmaceutical company consisted in a public reprimand, advertisement, and referral to the ABPI board, in order to consider "expulsion from the ABPI" [2].

The event that was strongly reprimanded by the PMCPA may be easily misinterpreted as an academic misadventure, therefore regulated by research governance processes. Instead, it represented a rare event of dubious clinical practice linked to illegitimate funding process that led to patient harm.

Undoubtedly, such event was enabled by insufficient governance processes. The ruling had clearly exposed that a protocol consisting of the novel combination of well-established immunosuppressants, initially considered as experimental, subsequently became the TxC official protocol for the prophylaxis of acute rejection in KTLD.

Table 2. Association of the British Pharmaceutical Industry Clauses Breaches

Clause 2	Bringing discredit upon, and reducing confidence in, the pharmaceutical industry
Clause 9.1	Failing to maintain high standards
Clause 18.5	Failing to keep proper records of a payment that was inappropriately linked to the use of a medicine

The fact that the pharmaceutical company involved has admitted the breaches reaffirms the importance of an efficient governance process.

REVIEW OF KIDNEY TRANSPLANTATION OUTCOMES GOVERNANCE IN THE UNITED KINGDOM

The careful reading of the ruling [2] would inevitably lead to a multitude of reflections, extending from the purely scientific to the ethical and medico-legal aspects of KT practice. Presenting a forensic review of the event, with the clinical impact it did produce, is beyond the scope of this analysis.

Nonetheless, in light of the fact that such event is linked to an extraordinarily high BPAR rate in the first year post-KTLD, impacting on patients outcomes, and perpetuated for almost 3 years, it indicates that the efficiency and contemporaneity of KT governance processes in the United Kingdom deserve careful considerations.

The structure through which the governance of the KT services outcomes is regulated may substantially differ between countries. The outcomes of TxC are most commonly governed with the local and regional processes indicated by the commissioners of the service, with different degrees of influence and oversight exercised by the national transplant authorities (NTxA) and regulatory bodies.

In the vast majority of countries with active transplant programs, the NTxA according to their respective statutory duties produce highly detailed organ-specific outcome analysis [3]. These highly regarded reports are referred to as the standards by the commissioners and TxC in supporting the governance processes [4]. Such reports are generally available for both public fruition and contribute to international database platforms [5].

Quality Requirements and Measurements in the United Kingdom

In the United Kingdom, the activity of the TxC is supervised directly by the commissioners of the service. The NTxA maintains a monitoring role on the workload of the TxC and primary outcomes, without, however, a direct participation to the formal governance process of the TxC or its outcomes.

The governance of KT service reflects the contractual relation between commissioners and providers. In such legal contract, named service specification, it is stipulated that the organizations providing the KT service are expected to implement a "robust clinical governance structure" [4]. The quality requirements are identified and divided in 5 "quality domains."

The detailed outcome framework indicates, among the quality requirements, the criteria to ensure "optimal long-term function of the transplant and to minimise complications, side effects and co-morbidity of KT" [4]

Relevant to the case presented, it is also clearly indicated that TxC are expected to provide "effective immunosuppressive therapy" [4].

The quality measurements cover the 30 days, 1 year, 5 years PS and GS for all types of KT[4].

The TxC are expected to "provide accurate timely data" to the NTxA in order to enable the commissioners evaluating the outcomes. Therefore, it may be summarized that the accountability of the governance process remains in the remits of the providers, whereas the commissioners monitor the outcomes referring to the reports produced by the NTxA.

Current Limitations

The current system of governance is centered on the consolidated scientific validity of PS and GS rates and in defining the survival advantage of KT over other forms of renal replacement therapy.

However, the growing complexity of KT practice, together with the consolidated scientific knowledge, may not be fully reflected in PS and GS rates alone, despite including adequate adjustment for donor risk factors. Furthermore, referring to a national average of survival rates, albeit interesting, may have a limited application for the governance process, as the national average itself may not necessarily reflect a validated clinical benchmark.

The restricted binary evaluation represented by the survival or nonsurvival of patients and grafts may also contribute to substantial delays in evaluating those aspects of the service that ultimately will influence all of the survival rates and could potentially be successfully corrected.

The absence of intermediate measured outcomes that influence PS and GS may indicate a true limitation of the current governance processes. Notwithstanding the relevance of BPAR and graft functions indicating those parameters as contributory in predicting subsequent GS [6−8]; such parameters are not currently included among the quality measures. This is despite the fact that providers are contractually expected to deliver "optimal graft function" and "effective immunosuppressive therapy" [4]. Therefore, it appears as being rather contradictory that the current governance process does not contemplate valid measurements of relevant quality requirements.

This apparent vacuum of the governance process may reflect negatively on the completeness of the counseling and informed consent that all of the patients should receive regarding the general risks and benefits of KT. Also, evaluating the KT outcome only on survival rates implicitly may contribute to the establishment of a prescriptive rather than constructive process that, as already suggested, may actually be detrimental [9].

IMPROVING GOVERNANCE IN KIDNEY TRANSPLANTATION

Implementing an efficient and constructive governance in KT probably represents one of the most taxing duties of modern health care.

In order to enhance the efficiency of the current governance process and its alignment to our contemporary practice some necessary steps may be considered.

Defining realistic and stratified benchmarks of expected survival rates would represent an essential prerequisite to overcome the current reliance only on national survival averages. The benefit of referring to scientifically determined and stratified benchmarks is reinforced by the observation in the United Kingdom of substantial variations of survival outcomes between TxC, clearly demonstrated in the 5 years risk-adjusted GS from a deceased donor [3].

Also other parameters reflecting intermediate outcomes should be considered. Including the incidence of BPAR and graft functions to the PS and GS outcomes would certainly enhance the quality of the KT service governance, as much as it would respond to specific quality requirements already identified in the service specification.

On this regard, the accuracy of national reports demonstrates that appropriate stratification and adequate benchmarking may be achievable with the current level of data obtained from TxC and NTxA. Notably, the variations of graft function between TxC reported from professional bodies [10] represent a further indication for defining clear benchmarks also for those intermediate outcome measures not currently analyzed. It is relevant noticing that in the United Kingdom, >36% of the KT from donors after brain death were from donors considered at high risk, according to the UK Donor Risk Index [3,11,12].

Accurate benchmarking applied also to intermediate outcomes would also address the responsiveness of the process itself. Focusing only on survival rates, in fact, may divert the attention from those parameters that demonstrably influence the long-term outcomes (Table 3).

Table 3. Kidney Transplantation Quality Framework and Possible Improvements

Quality Requirements	Quality Measures	Reference	Possible Improvement
Optimal long-term function of the KT	PS 1 and 5 y GS 1 and 5 y	National average from NTxA annual audit	Including graft functions in the quality measures Benchmarking
Provide efficient immunosuppressive therapy	Not currently measured	No reference	Including BPAR rate in the quality measures Risk stratification Benchmarking
Minimize complications Side effects Co-morbidities after KT	PS 30 d GS 30 d	3 monthly report NTxA	Including intermediate outcomes (BPAR and graft functions) in the quality measures

BPAR, biopsy-proven acute rejection; GS, graft survival; KT, kidney transplant; NTxA, national transplant authorities; PS, patient survival. Adapted from Service Specification.[3]

Inevitably, obtaining more information related to the performances of TxC will require more detailed analysis. Operating a regular peer-reviewed performance monitoring and improvement system would allow analysis of the more granular details of the outcomes self-reported by TxC to the NTxA. Such governance system is already in place in the United States, where the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing rely on self-reporting and site surveys to support the continuous improvement of the KT services.

DISCUSSION

Improving the governance of KT may be possible due to the availability of high-quality reports, constructed with data diligently communicated by TxC and rigorously analyzed by the NTxA. The quality requirements indicated by the commissioners reproduce the vision of an efficient and dedicated service. However, aiming for the highest standards of service requires better defined measurements. Arguably, the scientific achievements may influence the quality of care, provided that those achievements may be reproducible and adhered to as a standard.

In the United Kingdom, as in many other countries with a prominent transplant program, the national health service organizations providing KT services are expected to establish a "robust governance." The historical dilemma "*Quis custodiet ipsos custodes?"* would appropriately apply to the KT service governance.

In order to address Plato's question, it would be appropriate to establish whether KT should be considered a national resource, requiring a national oversight of outcomes, or instead, a regional service requiring only monitoring of the commissioners. In this context, it would be relevant to highlight that in recent years KT has substantially surpassed all of the other forms of renal replacement therapy in the United Kingdom (Fig 1) [10]; furthermore, considering that the resources for renal replacement therapy are not infinite, it would be reasonable considering KT as a national resource.

Independent of the fact that the governance of KT services may continue being administered solely by TxC or potentially considering the development of new formulas, in conjunction with the Commissioners and NTxA, it would be beneficial to reach a consensus on the desirable improvements, with the active involvement of the wider stakeholders of the KT services, including patients and professional bodies.

Advocating the direct involvement of NTxA in the local governance processes, such as annual audits and protocols implementation, is probably not desirable and impractical. Instead, strengthening the NTxA role in the definition of standards, as well as assisting TxC and Commissioners in the adherence to the same, would represent a safe evolution of the current governance process.

Internationally, there are several examples of national governance of KT Services. A system similar to the one in place in the United States, where federal oversight for KT is offered via the United Network for Organ Sharing and OPTN, may be certainly reproducible in the United Kingdom. Relevantly, the OPTN brings together medical professionals, transplant recipients, donor families, and representatives from transplant associations to develop organ transplantation policies. Furthermore, in the United States, the Centers for Medicare & Medicaid Services also provides regulatory oversight with primary oversight for organ procurement organizations. They rely in large part on both OPTN and national data from the Scientific Registry of Transplant Recipients to conduct that oversight.

In the United Kingdom, organ donation and procurement are already nationally commissioned and regulated. It may therefore be considered a natural evolution to also have the KT outcomes regulated by a national governance process aimed to safeguard patients and professionals.

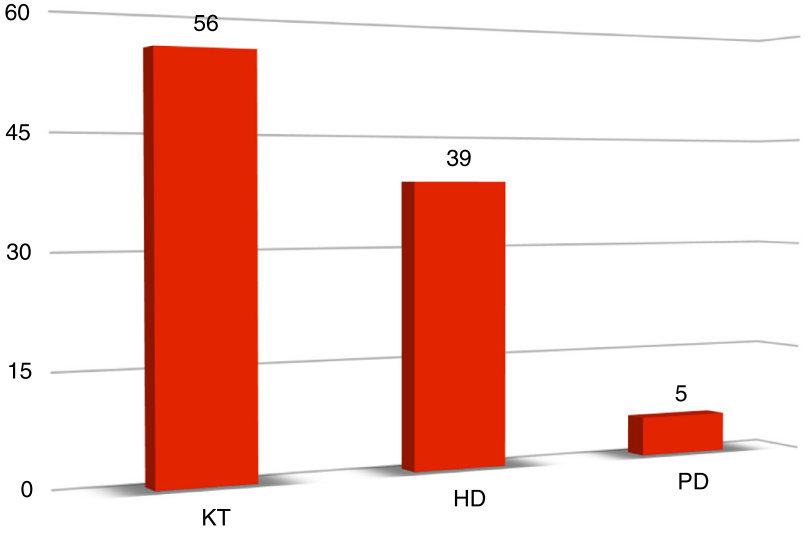

Fig 1. Adapted from Renal Association 22nd Report. Rate of treatment modality of adult patients prevalent to RRT on 31/12/2018 in the UK.

KT= Kidney Transplant; HD= Haemodialysis; PD= Peritoneal Dialysis

With regard to the case presented, it may be argued that high BPAR rates perpetuated for 3 consecutive years might have been addressed and corrected as required by an efficient peer-reviewed national governance system.

The advancements in guaranteeing the highest quality of patient care would also contribute to a successful application of the principles of value-based health care to KT practice. The "value" of KT will require being contextualized in the wider treatment options and strategies offered to patients with end-stage kidney disease [13]. The conceptual shift from the current fee-for-service (or tariff-for-service) to value-for-service would support the integration of intermediate outcome measure as KPI to the current survival rates, as more comprehensively will reflect on the requirements of the suggested domains of value-based health care, condensing the benefits for patients, society, providers, suppliers, and payers [14].

In conclusion, improving the current governance system is achievable without requiring revolutionizing the entire process.

The occurrence of adverse events indicates that improvements should be considered, as much as such events may be subject to indiscriminate generalizations and distorted magnifications, consequently leading to substantial risk of undermining the public perception of SOT practice nationally and internationally.

The "duty of candor binding our professional integrity to our patients while facing negative outcomes should also instigate the appropriate reflections on actual or possible systemic limitations [15] of the current governance process. Focusing our reflections arising from adverse events toward a better efficiency and transparency would safeguard the future developments of the services offered by a professional community that requires and undoubtedly deserves public support.

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