Calcimimetics and other simple pharmacological interventions do not work in dialysis: what can we do about it?

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Abstract

In this commentary, we explore the use of simple pharmaceutical interventions in dialysis patients and highlight the relative lack of efficacy for this approach to improve clinical outcomes. We suggest the development and evaluation of more complex and context-dependent strategies that might improve the aspects of dialysis most relevant to both patients and health systems.

Key words: Dialysis, Epidemiology, Outcomes

Against all hope, cinacalcet does not improve the lives of our dialysis patients. The recent Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, which compared cinacalcet with placebo in 3,883 dialysis-dependent patients with elevated serum parathyroid hormone levels over 5 years, confirmed what we already suspected from previous calcimimetic trials (1). Given routinely, cinacalcet does not improve survival and may increase patient morbidity through hypocalcemia, nausea and vomiting (2). Despite exciting initial evidence that cinacalcet alleviated perturbed serum parathyroid hormone, phosphorus and calcium levels (unlike vitamin D compounds and phosphorus binders before it) (3), the drug has not gone on to fulfill its early promise of better survival when measured against patient outcomes. Cinacalcet, a drug that started out so encouragingly, has ended up being just the next in a series of therapeutics without clear evidence for widespread use in dialysis, immediately after statins (4), epoetins (5), vitamin D compounds (6) and phosphate-binding agents (7). However, lack of evidence during cinacalcet development has not stopped us prescribing it by the bucket load. Despite a Cochrane review showing no strong evidence for effectiveness in 2006 and before the results of EVOLVE were released (8), cinacalcet became the single most expensive drug in dialysis in the United States in 2010 (9), accounting for over a quarter of a billion US dollars of health expenditure each year. The lack of progress in dialysis has not only been in the domain of pharmaceuticals. We have witnessed similar disappointing outcomes for nonpharmacological interventions, including higher dialysis dose (10) and early dialysis start (11). While we are fortunate to have tenacious pioneers who fund and conduct large-scale trials of new strategies in dialysis, our journey from promise to lack of evidence, accompanied by widespread prescribing, is one the nephrology community has now been on countless times before.

We embark on this journey repeatedly because of the ever-present awareness that our dialysis patients experience appalling mortality and profoundly impaired quality of life (9), which impels us to explore new ways to improve our patients’ lives. We begin all over again by looking for novel potential determinants of health – in other words,
clinical features that are associated with poor outcomes for dialysis patients – that give us testable targets for drug or intervention development. And we clearly have no lack of potential candidates in the field of nephrology because the highly perturbed and complex physiology of advanced kidney disease combined with our penchant for systematically measuring and recording clinical characteristics of dialysis patients and treatment within registries provide us with nearly endless data sources to scour and evaluate. In the case of cinacalcet, evidence from nonrandomized studies showing that elevated serum parathyroid hormone and phosphorus were associated with death spurred us on (12). However, we lost our way as a medical community in the story of cinacalcet and other strategies because we used interventions before we had sound evidence. Our collective belief that evidence of an association between a clinical attribute (low hemoglobin or elevated parathyroid hormone) and poor outcomes was the end, not the start of our journey, combined with clinical necessity, led us to conclude that the corrective treatment would provide the improvement in dialysis outcomes we urgently sought, and that we should use these interventions while waiting for the proper evidence (if any) to become available. Nowhere was this misconception more starkly demonstrated than in the story of epoetin (13), where anemia treatment increased mortality, rather than improving it, despite a preliminary hypothesis to contrary. This well-trodden voyage – finding a single novel determinant of health, developing and using an intervention to modify that determinant, and then finding the intervention does not work and sometimes even does more harm than good – has been traversed time and again in the field of dialysis. We have potentially wasted billions of dollars and placed our patients’ lives at risk in the intervening period, between finding a new potential treatment and having high-quality evidence to guide our practice. Why do we keep doing this, and more importantly, why is it that promising interventions do not work for our dialysis patients? Are we being too simplistic? Are we making too many compromises to simplify our patients’ lives and our own (e.g., with thrice weekly dialysis instead of daily)? Are we listening to our patients? How can we change the course of our recurring journey? It appears that simple interventions out of a bottle or syringe fall well short as answers to improving dialysis outcomes, despite the clinical urgency. Because the physiology of the dialysis patient is so perturbed in ways that we fail to completely understand, a single pharmaceutical such as cinacalcet insufficiently modifies the complex causal pathways of morbidity, to result in any clinical effect even in large well-conducted trials and meta-analyses. Hoping that a single intervention that can be comfortably administered and whose surrogate effects can be promptly measured could combat the severe and numerous abnormalities that accompany advanced kidney disease may be a bit like rearranging the deck chairs on the Titanic; it provides superficial comfort but is insufficient to result in deep and important changes in relevant physiological abnormalities associated with dialysis, to alter the clinical course of our patients. Worse, our preoccupation with such interventions may even be distracting us from identifying more complex but ultimately more effective strategies.

Clinical parameters associated with dialysis are measured regularly and repeatedly. These include serum phosphorus, parathyroid hormone, hemoglobin and cholesterol, and dialysis dose and flux, to name a few. While these are all associated with survival and are often used to measure the quality of our practice and guide reimbursement, it is sobering to consider that not once have we shown that modification of any of these aspects of our practice improves our patients’ lives. While these parameters are linked to patient outcomes, they appear not to be sufficiently causal. Would our money be better spent on something else? This reductionist approach to improving care – the philosophical position that a complex system is simply the sum of its parts – is not working in research into kidney disease or elsewhere in health care. We are acting as if altering individual physiological components observed in dialysis patients is sufficient to change outcomes. In fact, like the rest of life, dialysis is a complex system (both within the human body and within health care networks), and our focus on isolated phenomena such as serum parathyroid hormone or anemia or dialysis dose, as a remedy to patient-relevant outcomes, has simply not succeeded to date. The answers to what works in dialysis are likely to be much more complex than the many surrogate markers of health status we use, but as a community we seem to focus on these factors in the absence of something better. In fact, when we ask patients, these dialysis attributes (hemoglobin, parathyroid hormone levels, dialysis dose, etc.) do not even appear among those that are important to them and their caregivers; they are solidly trumped by factors such as survival, convenience (including dialysis at home), treatment flexibility, integrated care, a fistula, the ability to travel and dialysis-free days (14).

Listening more closely to the views and experiences of our patients could help us change our dismal record in improving outcomes in dialysis. By focusing on aspects of care that are most relevant to patients and their families, we may start to make new inroads into improving dialysis treatment by designing interventions that work for the outcomes that patients
value. We suggest complex rather than simple interventions may hold the promise here, ones that are “built up from a number of components which may act both independently and inter-dependently” (15), and for which the component(s) of the intervention that most contributes to outcomes may be uncertain. Complex interventions, which include differing ways of delivering care, will necessarily be nested within complex health systems and will need to be adaptive to their environment (unlike a drug which tends to be used similarly in differing health contexts). In dialysis, more complex interventions are showing the potential to improve lives and survival, including ways of delivering hemodialysis beyond the current mainstream model of short periods of dialysis 3 times each week. Longer hours (16) and more frequent (17) dialysis are promising strategies within the North American context, and to achieve both, home dialysis (increasing treatment convenience and flexibility) is worthy of further study, although provider (18) and patient (19) acceptance of such interventions may not be guaranteed and these require substantial training and support to succeed even in the earliest phases of development. Since an existing culture and habit of doing dialysis in operationally efficient ways is difficult to change, newer patient-friendly dialysis technologies may also be needed to facilitate patient goals, although, e.g., the experience of universal community dialysis in Christchurch, New Zealand, suggests a health system philosophy may be more important than smaller dialysis machines in achieving home-centered dialysis care. Beyond dialysis, it is clear that dialysis patients’ lives are profoundly improved by transplantation (20), and complex policy changes combined with research will be necessary to make kidney transplantation more available to more patients with chronic kidney disease. In the face of the twin tsunamis of obesity and diabetes mellitus, effective chronic kidney disease prevention rather than simple interventions for dialysis holds a much greater potential to improve lives and should hold sway for policy makers and research funders.

With cinacalcet, like many drugs before, we have embarked on a road to improving the lives of dialysis patients using a simple intervention and been called up short again (and spent a great deal of money and other resources in the process). Although the dire outcomes of patients treated with dialysis (and surrogate-based measures of quality to drive reimbursement) compel us to use interventions before they are proven to be effective or not, we need to steer a new direction. Strengthened joint partnerships between research funders, health systems and patients will be needed to prioritize the evaluation of complex health strategies that reduce the need for dialysis and improve the aspects of care that dialysis patients most value, and stop us treading this well-worn path too many more times.

And what about ourselves as a practicing community? Maybe we need to deepen our collective understanding about cause and effect, to know better when there is enough sound evidence to write prescriptions for the latest pharmaceutical development or when to demand and await something more complicated but potentially effective for our patients. Perhaps this will require more fraternity between the medical, political and patient communities; together we can reach out of our comfort zones and foster new challenges for the good of a system that poses a high burden and unsustainable costs on patients and society.

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