Survival Benefits with Vitamin D Receptor Activation: New Insights Since 2003

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The introduction of calcitriol followed by several of its analogs in the 1990s made vitamin D receptor activators (VDRA) the cornerstone of therapy for secondary hyperparathyroidism. The 2003 publication of the first major epidemiologic study describing the association of VDRAs with survival in ESRD has raised the awareness of the nephrology community about the potential impact of these agents on morbidity and mortality. This study was followed by numerous other epidemiologic studies which attempted to address the inherent shortcomings of observational studies by using sophisticated statistical methods. The complex nature of the statistical designs applied by some of these studies has led to some confusion about how to interpret the results, and how to use the results in a way that offers the most help for patients, but does not impede future scientific research. This report presents a discussion of relevant studies examining the association between VDRA and survival, with the goal to examine shortcomings that still exist in the knowledge on this subject. Special emphasis is placed on the discussion of studies with discrepant results to highlight remaining controversies and to emphasize areas in need of further research. Not withstanding all of the limitations of epidemiologic studies, the preponderance of evidence favors a survival benefit for ESRD patients treated with VDRA. This should provide a powerful impetus to investigate in clinical trials the risks and benefits of VDRA administration as a means to prolong survival.

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RCT, randomized controlled trial; ITT, intention-to-treat; MSM, marginal structural model; IV, instrumental variable.
it found that the administration of paricalcitol was associated with 16% lower all-cause mortality. The study was designed to test the hypothesis that the use of an analogue of calcitriol (paricalcitol) with fewer undesirable biochemical effects (such as hypercalcemia or hyperphosphatemia) may be associated with better clinical outcomes. To differentiate patients receiving the two different drugs an “as treated” analysis was favored over an “intention-to-treat” design, meaning that patients who were started on one or the other medication were removed from analyses (censored) if and when their treatment was stopped or was switched to the opposite drug. In a second analysis, patients who switched treatments during the study period were compared separately; this analysis also showed an association between paricalcitol and lower mortality, but implied that in an intention-to-treat design (where those who switched treatments would have been left in the original exposure group) the survival advantage associated with paricalcitol use would have been attenuated. By virtue of its design the Teng et al. study (15) raised a number of questions and spurred multiple publications aimed at answering these by examining different patient populations, different drug exposures or different end points and by utilizing more sophisticated statistical methods (Table 1).

**Active Vitamin D: The Argument for Class Effect**

One important question in the wake of Teng et al. (15) was whether the use of any VDRA could be associated with better survival when compared with no use, especially since a survival advantage of paricalcitol over calcitriol was not replicated by subsequent studies (16,17). A class effect of VDRA seemed plausible based on the complex biologic actions of vitamin D shared by all agents in this class (18,19). Essentially all of the epidemiologic studies that followed Teng et al. (15) have examined outcomes associated with the administration of any VDRA compared with no administration (Table 1). The first major study to examine this issue was published by the same group of authors (Teng et al. [20]) 2 years after their original publication. As opposed to their 2003 study (15) the authors used this time an intention-to-treat design and employed time-dependent analyses to account for temporal changes in several relevant confounders. Furthermore, to minimize selection bias and to address the problem of time-dependent confounding the authors also constructed marginal structural models (21,22), and performed facility-level matching of patients to account for the unmeasured impact of unequal care provided at certain facilities. This study indicated a significant association between VDRA use and lower mortality, irrespective of the statistical models used. In concert with these findings several other studies published over the subsequent years have shown similar findings, most using the same or similar sophisticated methodologies (Table 1) (4,16,23,24). A notable exception was the study by Tentori et al. which analyzed data on 38,066 prevalent dialysis patients enrolled in all three phases of the Dialysis Outcomes and Practice Patterns Study (DOPPS) (17). This latter study also used complex statistical methods including baseline and time-dependent Cox models, as-treated and intention-to-treat analyses, marginal structural models and an instrumental variable. While their time-dependent Cox models and marginal structural models indicated lower mortality associated with VDRA use, no such advantage was seen in baseline Cox models or with the use of an instrumental variable (17). The authors emphasized the instrumental variable which was used for the first time to examine VDRA (a more detailed discussion of which is provided later) to explain their discrepant findings, but this does not explain why they also failed to detect a significant association between VDRA use and survival in their conventional baseline Cox models. The discrepant findings of the baseline Cox models in the Tentori et al. study (17) compared with other observational studies (4,16,20,23–27) could have been a result of differences in the studied patient populations and/or practice patterns; but the discrepancy between baseline Cox models and other models within this study also suggests the possibility for inadequate accounting for temporal changes in key confounders and/or selection bias in the baseline Cox models.

**What Dose of Active Vitamin D Is Ideal to Maximize Survival Benefits?**

Present clinical paradigms of VDRA administration ask for dynamic dose adjustments based on changes in PTH levels, which results in patients with the highest PTH receiving the highest doses of VDRA. Furthermore, metabolic side effects of VDRA also develop in dose-dependent manner, with dose-reduction or cessation of VDRA administration occurring in patients who develop hypercalcemia and/or hyperphosphatemia. The complexity of the clinical paradigms aimed at controlling SHPT makes it difficult to discern the impact of various doses of VDRA on survival from epidemiologic data. Studies that examined the administration of any dose of VDRA versus no VDRA administration have described survival benefits even in patients with low PTH and high calcium and phosphorus (20,25,28), suggesting a benefit that is independent of metabolic effects. However, these findings do not allow the disentanglement of the potential benefits of higher doses of VDRA from the potential harm caused by their metabolic side effects. Studies that examined the association of various doses of VDRA on survival described a gradual attenuation of the mortality benefit in patients receiving higher doses of the studied medications (4,24). Recognizing the confounding of this association by the higher PTH levels triggering the higher doses of VDRA Shinaberger et al. examined the associations of the paricalcitol-PTH ratio with mortality, which incorporated into one variable the weekly dose of paricalcitol and the PTH level that triggered the decision about the dose (29). This study described a linear increase in survival with higher levels of the paricalcitol-PTH ratio, supporting the hypothesis that the attenuated benefits of higher VDRA doses seen in previous studies might have occurred because of the deleterious effects of the higher underlying PTH levels of these patients. Postulating a survival benefit that is independent of PTH levels implies that the application of VDRA should not be restricted to patients with SHPT, and argues in favor of establishing different markers to determine an indication for VDRA use and to measure their therapeutic effects. An obvious choice could be the serum
level of 1,25(OH)₂ vitamin D: levels below 13 pg/ml have been associated with higher all-cause and cardiovascular mortality in a cohort of 825 incident hemodialysis patients who were not treated with VDRA, but not in those subsequently treated with such agents (30). Since treatment with VDRA in this study was not restricted to patients with low 1,25(OH)₂ vitamin D levels, inferences from it about the utility of using such levels as a therapeutic indication are indirect at best. This study also did not measure serum 1,25(OH)₂ vitamin D levels after treatment with VDRA, thus it remains unclear what levels of this marker would have to be targeted to maximize survival benefits and minimize unwanted biochemical side effects. It is also unclear how calcitriol analogues would be incorporated in a treatment paradigm based on 1,25(OH)₂ vitamin D levels, as their administration tends to further lower circulating levels of native 1,25(OH)₂ vitamin D (31), thus rendering it useless as a marker of therapeutic effect for these agents. Finally, the lack of a reliable and reproducible assay for the measurement of serum 1,25(OH)₂ vitamin D would make it practically challenging to implement such a strategy. Recently TNF-α-converting enzyme (TACE) levels have been suggested as a possible alternative means to monitor therapeutic effects in those treated with VDRA (32,33), but the validity of this physiologic approach requires substantially more investigation.

Another way to identify therapeutic indication and monitor benefits is to determine suitable surrogate markers for a survival benefit and examine the effect of various VDRA doses on these. Current, mostly industry-sponsored studies examining the effects of VDRA on left ventricular hypertrophy, inflammation or cardiovascular calcification (ClinicalTrials.gov identifiers: NCT00428246, NCT00796679, NCT00752102) are intended to test hypotheses based on biologic mechanisms of action of VDRA (18), but the validity of this physiologic approach requires substantially more investigation.

Can Observational Studies Replace Clinical Trials?

Clinical trials are considered essential to establish cause-effect relationships between an exposure and an outcome. Observational studies are not considered adequate to this end, mainly due to our inability to assure that observed outcomes are indeed solely the result of the studied intervention and not some other unknown or unmeasured factor that may have prompted the application of the intervention to start with. All of the observational studies that examined survival benefits of VDRA suffer from various shortcomings compared with clinical trials (Table 1). A number of statistical techniques have been developed to address these shortcomings of observational studies and thus to mimic the design of randomized controlled trials; some, such as simple adjustment for baseline confounders, propensity score-matching or the use of marginal structural models and g-estimation are more sophisticated and are considered more appropriate to address issues such as confounding by indication or time-dependent confounders, propensity score-matching or the use of marginal structural models and g-estimation (34). All large observational studies that used time-dependent analyses (4,16,17,20,23,24), propensity score-matching (24), or marginal structural models (17,20) have described significant associations between the administration of VDRA and survival. Of all these statistical techniques marginal structural models combined with an intention-to-treat design are thought to most closely mimic randomized controlled trials (21,22), but only as long as all of the patient characteristics that drove the use of the medication and that are relevant to the studied outcome are known to the researchers and are appropriately accounted for in the analyses. The problem with observational studies is that such knowledge cannot be guaranteed, and hence the potential presence of unmeasured confounders prevents us from concluding causation even from studies using such sophisticated methods (Table 1).

A technique that can address unmeasured confounders is the instrumental variable approach (35). This method consists of identifying a so called instrument, which is a variable that satisfies the following criteria: (1) It defines the intervention of interest (e.g., VDRA administration); (2) It affects the outcome (e.g., mortality) solely through the intervention of interest; and (3) The outcome and the instrument share no common causes (i.e., lack of confounders) (35). If one can than show that such an instrument is associated with the outcome, this can be construed as proof of a causal relationship between the actual intervention of interest and the outcome. An example of a perfect instrument is in fact the random treatment allocation in a clinical trial; one can also be occasionally defined for observational studies in cases where a natural “randomization” of a characteristic such as a genetic trait occurs at birth (such studies are also called Mendelian randomization studies) (36). Researchers have attempted to find instruments that are not determined by nature or by randomized interventions for use in observational studies to bypass the need for randomized controlled trials (35). Such an attempt was made by Tentori et al. in a recent study where the percentage of VDRA use in a given hemodialysis center served as the instrumental variable (17). The authors of this study failed to detect a significant association of their instrument with mortality and concluded that such lack of association questions the validity of all of the other observational studies of VDRA. The criticism of the instrumental variable approach in general is that it is difficult to tell if the chosen instrument is indeed conforming to the basic requirements that make it a valid tool; in the case of the Tentori et al. study one could imagine that dialysis units with higher rates of VDRA use may provide different care in other ways too, which in turn could also affect outcomes independent from active vitamin D and thus violating condition no. 3 of a proper instrument (common source with the outcome). The instrument chosen by Tentori et al. (17) could in fact be construed as an ecologic study rather than a valid instrumental variable, and as such it is prone to a number of additional biases (37). Furthermore, it is unclear to what extent issues affecting the baseline Cox models (17) of this study (which were discussed above) could have impacted the results of the instrumental variable, which utilized base-
line data to define usage of active vitamin D and to adjust for confounders. Based on the above consideration it is the author’s opinion that the Tentori et al. study (17) can hardly be construed as definitive proof against the benefit of VDRA on survival.

Should we thus conclude that the evidence from observational studies is so overwhelming, and the biology of vitamin D is so compelling that we don’t need clinical trials to prove that VDRA indeed causes better survival? This argument should not be accepted in the wake of recent clinical trials examining treatment of anemia with erythropoesis stimulating agents showing no benefit and even harm (38–41), and thus refuting the results of multiple previous observational studies. VDRA should be held to the same standard of evidence, and its long term benefits (and risks) should be tested in properly designed clinical trials. An obvious stumbling block is the ethical dilemma posed by a placebo-controlled design, as patients receiving placebo could be deprived of the PTH-lowering benefits of VDRA; conversely patients receiving VDRA could be harmed by oversuppression of PTH. One could argue that the benefits of “ideal” PTH levels are far from proven when it comes to survival, but it is easy to see how the attention devoted to SHPT and its therapies in the past two decades (14) could impede successful enrollment of patients in such a study. A possible solution could be the application of nonvitamin D based strategies to control PTH equally in the two arms of such a study, or to use active comparators. Such an attempt was made by launching in 2003 a randomized controlled trial of paricalcitol versus calcitriol in ESRD patients (ClinicalTrials.gov identifier: NCT00062699). Perhaps as a consequence of overenthusiastic interpretation by US Nephrologists of the Teng et al. study (15) which was published the same year, this clinical trial failed to enroll adequate numbers of participants and was ultimately terminated in 2006. It is also possible that performing a large and expensive study of survival with VDRA was premature; such studies may become more feasible once we have a better idea about what the ideal target populations, VDRA agents, and doses might be to achieve maximum benefits. For the time being we have to come to terms with the fact that VDRA should not yet be applied with the (even tacit) intent to improve survival, but we should also not give up on the promise that it may one day become a much-needed panacea for our patients.

Conclusions

Much has been learned about VDRAs since the publication of the first large epidemiologic study on their association with survival in 2003. We are now at a point where further knowledge gained from observational studies is becoming limited and the overemphasis of such studies can indeed become counterproductive unless we shift our focus to clinical trials to test the hypothesis that VDRAs may help our patients beyond lowering their PTH levels.

Disclosures

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