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The Downsides of a Major Medical Advance

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Abstract

When positive, the results of randomized controlled trials designed to evaluate the effectiveness of new options are released with great fanfare. This is especially true for difficult to treat conditions for which there are few treatment alternatives. This scenario recently played out at the 2009 American College of Rheumatology National meeting when the long anticipated RAVE (Rituximab versus Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitis) trial results were announced. Since then the results of the RAVE and RITUXVAS trials have demonstrated that rituximab is as effective at inducing remission in patients with ANCA positive vasculitis as cyclophosphamide. Prior to these trials, cyclophosphamide was the option of choice for this potentially life threatening disease, and physicians have long hoped for a viable alternative given the significant toxicity associated with this medication, particularly infection, infertility, and cancer. While the results of the trial were justifiably received with great enthusiasm, practical clinical experience has revealed some noteworthy downsides to this important medical advance.

Systemic vasculitis is a rare but serious disease associated with a high risk of morbidity and mortality 1. Treatment includes both high dose glucocorticoids and immunosuppressive drugs 2. Cyclophosphamide has been considered the initial immunosuppressive agent of choice for patients with major organ involvement for over 40 years, and physicians caring for patients with vasculitis have long awaited the availability of a safer alternative. Thus the results of the RAVE (Rituximab versus Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitis) trial, presented at a plenary session at the American College of Rheumatology Annual meeting in November 2009, were received with great enthusiasm. The RAVE trial was designed as a multicenter, randomized, double blind, placebo controlled non-superiority trial of rituximab (375mg/m² iv weekly ×4) versus cyclophosphamide (2 mg/kg po for months 1–3 months followed by azathioprine 2 mg/kg po for months 4–6) for the induction of remission in patients with ANCA-positive vasculitis 3. Both groups received high dose glucocorticoids tapered over six months. The objective of the study was to determine whether rituximab (a presumably safer alternative to cyclophosphamide) was at least as effective as cyclophosphamide at inducing remission defined by a Birmingham Vasculitis Activity Score of 0. The trial demonstrated that the two medications were equally effective [64% of subjects randomized to rituximab and 55% randomized to cyclophosphamide achieved remission (p=0.20)] thereby signaling a major medical advance in the treatment of vasculitis 3. The results of the RAVE trial and a second trial comparing four weekly doses of rituximab and two iv pulses of cyclophosphamide with iv cyclophosphamide for three to six months followed by azathioprine to induce remission in

renal vasculitis (RITUXVAS) 4 were recently published in the New England Journal of Medicine.

One month after the RAVE trial results were announced, I was asked to see a patient admitted to the intensive care unit with ANCA-positive vasculitis while attending on the inpatient rheumatology service. The patient was in her early forty's, previously in excellent health, until she began to develop general malaise, cough, and progressive shortness of breath on exertion over a four to six week period. An episode of hemoptysis prompted her to seek care. On presentation to the hospital she was found to have diffuse pulmonary infiltrates on a CT scan and to be in acute renal failure. Once the diagnosis was confirmed, I settled into a chair and began the discussion with a description of the RAVE trial. Since then, I have become increasingly more cognizant of the downsides of this major medical advance.

Prior to completion of the RAVE and RITUXVAS trials, the process of initiating treatment for patients with a confirmed diagnosis of moderate to severe systemic vasculitis was straightforward and consisted of obtaining consent for high dose glucocorticoids and either intravenous or oral cyclophosphamide. In contrast, treatment planning for vasculitis now involves a choice between two rational options and therefore necessitates a collaborative decision making process between the physician and the patient 5. Collaborative decision making requires that physicians first inform their patients of the relevant risks and benefits associated with each option and subsequently elicit and incorporate patients' preferences into the treatment planning process. Several factors contribute the difficulty of collaborative decision making in this particular scenario.

Given the equivalent rates of remission induced by both treatment regimens, the decision of which treatment to initiate (assuming the patient has no contraindications to either option) rests on how patients value the differences in the risks of adverse events of the two medications*. The RAVE and RITUXVAS trials, which are the only head to head comparisons of cyclophosphamide and rituximab in any disease, demonstrated no significant differences in toxicity between the two options. Yet, physicians "know" that there are significant differences between these two drugs. The rationale for the trials was, after all, to determine whether rituximab-based treatment regimens were safer than prolonged use of cyclophosphamide. Most notably, rituximab was expected to, but did not, result in fewer (bacterial) infectious complications. Should physicians, therefore, based on the RAVE and RITUXVAS trial results, describe both drugs as being associated with the same incremental risk of infections? Or should we state that while infections rates were equivalent in the trials, numerous other studies (using cyclophosphamide in comparable doses) suggest that the risk of infections is higher with cyclophosphamide 2· 6? These two messages are likely to result in very different risk perceptions and preferences.

While randomized controlled trials would not be expected to generate data related to rare adverse events, one of the major concerns related to the use of cyclophosphamide is the increased risk of cancer, particularly, bladder cancer, lymphoma and leukemia 7· 8. The increased risk of cancer associated with cyclophosphamide, when used for the treatment of noncancer-related conditions, has been seen in patients using cyclophosphamide for two or more years. In contrast, current regimens attempt to limit use to six months or less and subsequently switch to a less toxic immunosuppressive drug such as azathioprine. Whether, and by how much, current regimens of cyclophosphamide are associated with an increased risk of cancer is not known. Faurschou et al 9 examined the risk of cancer in a cohort of patients with Wegener's granulomatosis and found that the risk was not increased in patients

*The route of administration for both drugs also differs.

taking shorter courses (less than 36 grams) of cyclophosphamide. Therefore, in presenting the contrasting features between rituximab and cyclophosphamide, should we continue to inform our patients of an increased risk of cancer associated with the latter? If yes, what is the magnitude of risk that should be attributed to cyclophosphamide in this setting? Defaulting to the use of verbal phrases alone (e.g. possible, rare or small risk) to compensate for the lack of data in this scenario is likely to be counterproductive, as risk formats which exclude numerical data tend to increase patients' worry about risk 10.

Even more difficult to disclose is the extremely rare, but dreaded risk, of progressive multifocal leukoencephalopathy (PML). The reported cases of PML in rheumatoid arthritis patients treated with rituximab and the resulting FDA black box warning, mandate disclosure of this risk in all patients regardless of the indication for treatment. Challenges of disclosing the risk of PML derive from the difficulty people have understanding extremely small probabilities (e.g., the chance of being hit by lightning) and the fear associated with dreaded outcomes, especially those associated with cognitive disability and a risk of death. Numerous studies have shown that people's risk perceptions are influenced by the emotion they experience when faced with a specific image or scenario 11–13. This observation, referred to as the affect heuristic 12, explains why patients who have an extremely negative emotional response to a physician describing PML are likely to refuse rituximab whether the risk of PML is 1 in 100,000 or 1 in 1,000,000.

To the best of my knowledge, the risk of PML is not traditionally discussed prior to prescribing cyclophosphamide for vasculitis or other noncancer conditions such as lupus nephritis. Yet, the recent reports of PML occurring in patients on biologics has led to a renewed interest in the baseline risk of viral reactivation and increased awareness of cases of this devastating infection occurring in patients with autoimmune disorders treated with immunosuppressive agents including cyclophosphamide 14. Is it therefore appropriate to attribute the risk of PML to rituximab and not to cyclophosphamide? Is it in patients' best interest to attribute the risk of PML to the latter when we have not done so in the past?

The RAVE and RITUXVAS trials signal a very important advance for the treatment of patients with vasculitis. Now for the first time, there is a proven effective alternative to cyclophosphamide for patients with moderate to severe systemic vasculitis. This is especially important for women who may be particularly concerned about the risk of ovarian toxicity associated with cyclophosphamide and for patients who fail to respond, or who have already been exposed to "significant" doses of this medication. However, for treatment naïve patients, the availability of rituximab as a second option has introduced significant uncertainty, thus making the treatment planning process much more complex. Choosing between two options, each associated with rare but dreaded adverse events, is arguably a much more difficult task than proceeding with the standard of care. The uncertainty related to the attribution and magnitude of risk and the emotion associated with dreaded adverse events (including cancer and PML) make it extremely challenging to effectively inform patients without bias. Variability in treatment planning is expected given that patients' preferences for these two options will differ. However, variability should be due to differences in patients' values and not to differences in the content and manner in which physicians present information. Further data will hopefully provide more accurate information to facilitate informed and value concordant decision making in patients with systemic vasculitis.

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