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INVITED COMMENTARY

Rejection: the emperor's new clothes

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In 1837, Hans Christian Anderson published a Danish folk tale of a vain emperor who was promised a spectacular set of clothes by two weavers [1]. These garments would not be visible to people who were unfit for their positions, stupid, or incompetent. In reality, the weavers fooled the emperor, pretending to dress him in the new clothes yet not providing him anything at all. When he paraded past his loyal subjects, none wanted to admit that they did not see any outer clothes and be subject to ridicule. All, except a child who told the truth that the emperor had no clothes.

It is fitting that the group in Denmark now presents a detailed analysis of cardiac allograft rejection and the association with coronary vasculopathy as assessed by intravascular ultrasound (IVUS), from the SCHEDULE trial. In this issue, Nelson and colleagues describe a 76 patient subset of the trial with participants who had matched baseline, one as well as 3-year IVUS measurements, along with 3-year coronary angiography [2]. The IVUS studies were analyzed in a core laboratory and coronary angiography results were presented as well according to the International Society for Heart and Lung Transplantation (ISHLT) grading system for cardiac allograft vasculopathy (CAV) [3].

Previous reports from the SCHEDULE investigators noted a paradoxically higher incidence of moderately severe (ISHLT grade 2R or worse) rejection with everolimus but no difference in outcomes [4–8].The current study examines 3-year IVUS data with regard to rejection profile and finds surprisingly that repeated mild acute cellular rejection (ISHLT grade 1R) has no effect on the development of CAV. Furthermore, even more severe rejection (ISHLT grade 2R/3R) did not result in an increase in IVUS detected CAV by numerous core laboratory measurements. This finding was observed in patients in both study groups (those receiving everolimus as well as those on cyclosporine). Previous reports have indicated that the incidence of mild and moderate rejection (ISHLT grades 1R and 2R/3R) was significantly higher in the everolimus group than in the mycophenolate mofetil group [4,5]. However, in the current study, the proportion of patients with any degree of CAV at three years post-transplant was numerically higher in the ISHLT grade 0R group (40%) compared with the grade 1R group (24%) and the grade 2R/3R group (7%) ($P = 0.06$).

Rejection is a key issue in heart transplantation, being responsible for the demise of the first heart transplant

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patient, and there is no doubt that it is an important aspect of post-transplant care. Previous work has shown that moderately severe rejection is associated with worse outcomes including the development of CAV [9,10]. Newer immunosuppressant agents such as tacrolimus were approved after study comparing the rejection efficacy with cyclosporine [11]. Indeed, the current generation of drugs provides a low risk of rejection, creating a high bar for the entrance of other immunosuppressants [12].

Drugs such as everolimus are a good example of this problem. Everolimus has been studied in numerous heart transplant trials, with a consistent message [4,8,13]. The incidence of allograft vasculopathy as detected by IVUS is clearly reduced, though the risk of rejection is increased as compared to cyclosporine and mycophenolate mofetil-based regimens. Similar findings are seen with a tacrolimus-based platform [14–16]. Everolimus has been associated with delayed wound healing, and most recommend to delay initiation of this drug beyond the period of wound healing to avoid complications [17]. Use of everolimus allows marked reduction in calcineurin trough levels or complete avoidance of calcineurin antagonists, leading to improved renal function. Nevertheless, the drug is not approved in the United States for use in heart transplantation due to the excess of rejection but it is approved for kidney transplant recipients.

Perhaps, the time has come to see cardiac allograft rejection as the equivalent of the emperor's new clothes. As a transplant community, we have a huge fear of rejection, but this approach has not resulted in more than trivial improvements in survival over the last 20 years [12]. Innovations such as everolimus have achieved little uptake in many centers due to the fear of rejection, but the larger cause of death is CAV which is reduced by this agent. Similarly, the majority of post-transplant patients remain on corticosteroids even at 5 years post-transplant, ostensibly to prevent rejection, though the long-term effects are significant.[12] Despite evidence of the benefits of rapid steroid weaning, centers tend to adopt a protocol and not adjust with the risk of the individual patient [18–20].

Induction antibody therapy has been utilized to reduce rejection, though it remains controversial even now more than 50 years following the first transplant. [21] Most evidence suggests that induction therapy (daclizumab, basiliximab, or thymoglobulin) delays the onset of allograft rejection, but does not improve survival [22,23], and in one study, patients who received both daclizumab and cytolytic drugs experienced a higher mortality due to infectious causes [24].

The emperor is naked. Rejection is important, but it is not the essential clothing of the transplant recipient. As a field, we must focus on long-term survival which is the most important goal. We must recognize that the immunosuppressive therapies we select lead to substantial morbidities and lead to deterioration of the transplant recipient over time. Patients value quality and quantity of life, and slavish devotion to avoiding any allograft rejection has done nothing to further either of these goals. We should focus on choosing immunosuppression which has the least toxicities and best long-term outcomes. As a transplant community, we must demand the development of new immunosuppressive agents, and when ones such as everolimus are identified, preferentially use these in appropriate settings to minimize allograft vasculopathy and maximize patient and graft survival.

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