nucleic acid anti-miRs induced EMT with loss of E-cadherin. These observations were attributed to the loss of miRs-200 repression of Zeb1 and Zeb2, negative regulators of E-cadherin.\textsuperscript{14} Hajarnis \textit{et al}.\textsuperscript{13} provide evidence for partial collecting duct EMT on the basis of localized expression of the mesenchymal markers, Vimentin and Snail2, in a subset of collecting ducts after a global loss of miRNAs; although lineage tracing did not show transdifferentiation of collecting ducts into myofibroblasts. Given that partial EMT has previously been proposed as a potential driver of renal fibrosis, Hajarnis \textit{et al}.\textsuperscript{13} suggest that loss of miRNAs, particularly miR-200c, results in partial EMT in collecting ducts, causing dysregulation of adjacent interstitial cells and eventual progression to tubulointerstitial fibrosis. Although the \textit{in vitro} data are consistent with the idea that loss of miR-200c drives the collecting duct partial EMT, it remains unclear whether loss of miR-200c (or its two parent clusters) \textit{in vivo} is sufficient to initiate tubulointerstitial fibrosis. Other epithelial regulatory miRNAs, such as miR-9, that would otherwise repress E-cadherin are also probably compromised in these models.

Indeed, partial EMT was only observed in a subset of collecting ducts. The heterogeneity may reflect miRNA-mediated activity opposing EMT, or other intrinsic responses to loss of miRNA regulation in the collecting ducts. As an alternative interpretation, it is tempting to speculate that collecting ducts undergoing partial EMT could in fact represent a snapshot of dedifferentiating tubules that could contribute toward renal repair.\textsuperscript{1} Regardless, the exhaustive work of Hajarnis \textit{et al}.\textsuperscript{13} using these miRNA biogenesis mouse models represent the first study to elucidate the importance of miRNA biology in postnatal collecting duct homeostasis, and provides information that will aid the identification of potential anti-fibrotic miRNA candidates.

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DISCLOSURES

None.

REFERENCES


ABMR is rare in patients without preformed donor-specific antibodies (DSAs), but it occurs in up to 40% of patients after desensitization. Most importantly, maintenance patients may develop de novo DSAs, and late ABMR is thought to be one of the leading causes for graft loss. Today, treatment options are limited, and the development of successful treatment strategies for ABMR is an important unmet medical need in transplantation, which was already discussed in 2010.2 Since then, only one larger (n = 39) randomized clinical trial was published, showing no positive effect of the anti-CD20 antibody rituximab in the treatment of acute ABMR.3 Despite progress in the classification of ABMR4 and numerous publications on different aspects of ABMR,5 today, we still rely in our treatment decisions on data from small retrospective patient series with a low level of evidence.6 In this issue of the Journal of the American Society of Nephrology, the results from a large registry7 and a prospective randomized trial8 provide important new insights into the treatment of ABMR and may pave the road for future clinical trials in this indication.

To target antibody-producing plasma cells, several centers have advocated the use of bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma.9 Several patient series have suggested positive effects of bortezomib within multimodal treatment regimens with an acceptable safety profile. However, until now, good evidence on efficacy and safety from a larger cohort of patients with ABMR was lacking. In this issue, Eskandary et al.8 report the results of the first prospective, randomized, placebo-controlled trial of bortezomib in patients with late active ABMR. For the BORTEJECT Trial, they screened 741 kidney transplant recipients in their outpatient clinic and identified 111 (15%) patients with DSA, of whom 86 underwent allograft biopsy. Interestingly, 34 of 86 (40%) did not have histologic ABMR features in biopsy, despite the presence of DSA. Finally, 44 patients were randomized to either two cycles of bortezomib (n = 21) or placebo (n = 23). Contrary to previous retrospective studies, two bortezomib infusions had no effect on outcomes over 2 years of follow-up; GFR slope (−4.7 versus −5.2 ml/min per 1.73 m² per year), measured GFR, proteinuria, DSA characteristics, and histology or molecular rejection phenotypes did not differ between groups. As expected, bortezomib was associated with some gastrointestinal and hematologic toxicity.

Although the trial has some weaknesses, Eskandary et al.8 need to be congratulated for performing such a rigorous prospective, randomized study with careful study reporting and a thorough phenotyping, including state of the art serology, histology, and molecular markers. Potential criticism include low numbers; the trial design, which did not allow for any additional treatment (such as plasmapheresis or ivIG); and the fact that baseline immunosuppression was maintained rather unchanged. However, the advantage of this approach was the possibility to really assess the sole effect of bortezomib in a clean clinical trial design. In retrospect, the main problem of the trial was the good outcome of the control group, with only one graft loss and a rather stable clinical course. The outcome of the control group teaches us that many patients with DSA (even with signs of ABMR in biopsy) have an uneventful clinical course over years, making it difficult for any intervention to significantly improve outcome. Large numbers are needed to show potential differences in eGFR for patients with slow declining renal function. As a consequence, future trials should focus more on fast progressors, in whom it is worth treating ABMR at the expense of potential side effects.

The article from Viglietti et al.7 in this issue nicely complements this conclusion from the BORTEJECT Trial. They developed an excellent prediction model for the long-term outcome after treated ABMR. The authors used their large database with 1978 patients, of whom 312 patients (15.7%) developed ABMR. For this analysis, they included 278 patients with ABMR (on average, 9.2 months post-transplant) who were treated with a standard protocol consisting of steroid bolus (3 × 500 mg), four to five plasmapheresis sessions, repeated high-dose ivIG (2 g/kg), and two to four weekly doses of 375 mg/m² rituximab together with tacrolimus (6–10 ng/ml), 1.5 g/d MMF, and 10 mg prednisone maintenance therapy. They first developed a prediction model at the time of ABMR diagnosis, which included eGFR, histology (cg and IFTA score), and de novo DSAs (versus preformed DSA) and provided reasonable prediction capabilities for death-censored graft loss. The second dynamic prediction model included response to treatment after 3 months. It consists of eGFR and IFTA at diagnosis as well as changes in eGFR, MFI of immunodominant DSA, and histology (ptc score) 3 months after treatment. The model had better prediction properties and was validated in a second cohort of 202 patients. Critics may argue that clinicians always knew that patients with improving eGFR and decreasing proteinuria after treatment do better than patients who do not respond to treatment. The model also does not take severe side effects and/or patient death into account. Nevertheless, both prediction models will be useful for therapeutic decision making in clinical practice. The dynamic model allows us to group patients into those with high, intermediate, and low risks for graft loss. Such validated prediction models are a powerful tool for patient enrichment in future clinical trials, because they may help to identify those patients who need a therapeutic intervention most. In addition the data are extremely valuable for the design of clinical trials and power calculations, and they may provide the basis for future validated surrogate end points as discussed during recent conferences.4,10

However, good research manuscripts always leave us with new questions. (1) Are the prediction scores derived from a cohort with “Paris standard treatment” also useful in the prediction of outcomes for patients treated with bortezomib or other therapeutic interventions? Will the scores really help to find fast-progressing patients for future trials? (2) Will bortezomib eventually be useful as second-line therapy in high-risk patents, which do not respond to “Paris standard therapy”? Does bortezomib eventually need to be embedded in a multimodal therapeutic concept? (3) What is the place for rituximab3 in the treatment of ABMR in the context of the negative outcome
of a randomized trial? How do we define subgroups at the time of diagnosis who really benefit or who are unresponsive to rituximab? Is rituximab only useful in multimodal combination therapy? What evidence do we have that rituximab (what optimal dose?) really contributes to the success of the multimodal combination therapy? (4) Is ABMR really the leading cause of graft loss given the fact that the vast majority of patients in Paris and Vienna do not develop DSA or ABMR and that only 30% of those experience graft loss after 6 years? What about causes of graft loss in patients who are DSA/ABMR negative?

In summary, both manuscripts have set a new reference point, which will help us to systematically improve our outcomes step by step in future clinical trials. Given the low proportion of patients with DSA and the even lower proportion of patients with active ABMR in both large transplant centers, it is obvious that multicenter trials are needed to adequately address novel therapies. Inclusion and exclusion criteria can be on the basis of the lessons learned from both studies. Ideally, future models may also predict toxicity and help us to better balance benefits and risks to develop individualized treatment strategies. However, at the end, models can only assist in the design of more successful future prospective trials, which have to investigate new treatment strategies to improve outcomes for patients with ABMR.

REFERENCES


See related article, “Dynamic Prognostic Score to Predict Kidney Allograft Survival in Patients with Antibody-mediated Rejection,” and “A Randomized Trial of Bortezomib in Late Antibody-mediated Kidney Transplant Rejection,” on pages 606–619 and 591–605 respectively.

Making the Right Decision: Do Clinical Decision Support Systems for AKI Improve Patient Outcomes?

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The path toward new, effective treatments for AKI has been difficult, with a frustrating lack of progress and a litany of negative clinical trials.1–4 Faced with large numbers of patients with AKI who display startlingly poor outcomes, it is not surprising that clinicians and professional organizations have sought parallel ways to address this, including the International Society of Nephrology “0by25” campaign and the “Think Kidneys” national program in England. Current guidelines recommend various elements of supportive AKI care, but reports spanning different health care systems tell us that the delivery of these relatively simple measures in “real-life” clinical settings is often suboptimal.5 A number of factors may contribute to this: the silent nature of AKI coupled to competing priorities of coexisting conditions; time pressures of busy clinical staff; or a lack of awareness, training, or knowledge of AKI outside of specialty nephrology or critical care

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