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Urinary Soluble CD163: A Novel Biomarker Suggests Who Should Receive Glucocorticoids in IgA Nephropathy

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Several long-term cohorts have revealed that the outcomes of patients with IgA nephropathy (IgAN) are far worse than previously expected. With rapidly emerging clinical research, supportive therapy for IgAN has expanded from renin angiotensin system blockade to include sodium-glucose cotransporter 2 inhibitors, and endothelin A receptor antagonists.[1,2] Among specific subpopulations of patients with IgAN, low-dose corticosteroids, hydroxychloroquine, mycophenolate mofetil, B-cell targeting agents, and complement antagonists have also been explored as potentially beneficial interventions.[1] As with all new therapeutics, the risks of treatment, such as hyperkalemia, fluid retention, heart failure, hepatotoxicity, and infection, need to be balanced with the potential benefits for the patient. Optimizing IgAN treatment is notoriously challenging for clinicians; however, the current data derived from these clinical trials have been insufficient to develop a comprehensive algorithm to guide clinical decision making.[2–4]

The 2021 Kidney Disease: Improving Global Outcomes guidelines[5] outlined that glucocorticoids or mycophenolate mofetil may be used for patients with IgAN who remain at high risk of progression despite maximum supportive care, and that the use of these agents should be carefully considered, taking into account the patients' kidney function and the potential toxicity of these drugs. Caution is advised because immunosuppressive therapy, particularly glucocorticoids, can pose significant risks to patients with IgAN, as demonstrated by the TESTING study.[4] The crucial question then becomes, which patients are more likely to respond to glucocorticoid therapy?

According to a recent study,[6] patients with IgAN who experienced a decrease in proteinuria to less than 1.0 g/d, known as glucocorticoid responders, had a significantly lower number of fibroblast-specific protein 1–positive ($FSP1^+$) cells in their renal tissue than nonresponders. The amount of interstitial damage, the percentage of glomerulosclerosis per total glomeruli, and chronic inflammation all showed a positive correlation with the number of $FSP1^+$ cells. Cox regression analysis revealed that the number of $FSP1^+$ cells was the strongest and most significant predictor of corticosteroid responsiveness. Patients with IgAN who had >32.6 $FSP1^+$ cells/HPF at diagnosis were more likely to exhibit steroid resistance.[6] Nevertheless, $FSP1^+$ cells need to be detected from renal tissue, which is counterproductive to dynamic monitoring, and they only predict glucocorticoid resistance in patients with IgAN.[6]

In this issue of *Kidney International Reports*, a study by Li *et al.*[7] demonstrated that the urinary soluble CD163 (u-sCD163) correlated with both disease activity and treatment response in IgAN. In their cross-sectional analysis, baseline u-sCD163 levels in patients with IgAN were associated with renal macrophage infiltration, crescentic area, as well as active lesions. They also demonstrate that patients with high u-sCD163 levels have a lower probability of benefiting from supportive renin angiotensin system blockade alone, whereas the relative benefit of glucocorticoid therapy is much higher.[7] Compared to placebo, both full-

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dose and low-dose glucocorticoid regimens significantly lowered u-sCD163 levels, and reduction of u-sCD163 levels was significantly associated with a lower risk of kidney progression events, which included ^{3}40% reduction in estimated glomerular filtration rate, kidney failure, and death due to kidney disease.[7]

The findings of Li *et al*. are consistent with a previous study which demonstrated that higher intensity of glomerular CD206+ or CD68+ macrophage infiltration was associated with increased likelihood of response to immunosuppression.[8] Collectively, these studies suggest that patients with IgAN with renal active inflammatory lesions related to macrophage infiltration should receive early treatment with immunosuppression. The study by Li *et al*. extends our repertoire for identifying glomerular macrophage infiltration; though previously, this could only be confirmed histologically through kidney biopsy, we can now use u-sCD163 measurements, a far more practical tool for dynamic monitoring across varied clinical settings. This study has also demonstrated that this novel biomarker is extraordinarily stable over years of storage, which expands the potential for monitoring u-sCD163 to include centers with more limited resources by being able to reliably send out testing for this novel biomarker.

Several unanswered questions concerning the use of u-sCD163 as a biomarker for treatment selection and monitoring in IgAN patients remain. Can the magnitude of change in u-sCD163 predict the degree of response to glucocorticoids? Does increased u-sCD163 levels in glucocorticoid responders imply a relapse of IgAN? Will a significant decrease of u-sCD163 accompany a remission of proteinuria from supportive therapy alone? Can u-sCD163 levels be used as a biomarker for monitoring treatment response of recurrent IgAN in transplanted kidneys?

Another important concern in IgAN treatment is how to optimize regimens and promptly assess their efficacy as new therapeutic drugs become available. Targeted-release budesonide, a newer glucocorticoid preparation, has been proven to have good efficacy and lower side effects for IgAN treatment.[3] It will be interesting to see whether budesonide will also lead to changes in u-sCD163, allowing us to expand its use as a biomarker for predicting and monitoring response to this novel therapy. Questions also remain around monitoring treatment response when existing therapies are repurposed in the setting of IgAN. For example, when employing complement antagonists in patients with IgAN, which complement components need to be monitored? Our previous work using proteomics technology demonstrated that multiple complement components in the urine of patients with IgAN are correlated with their clinical and pathological parameters, suggesting a role for using these as biomarkers in IgAN management,[9] and further evaluation of these is needed. Whether u-SCD163 may also have a role in predicting and monitoring response to newer therapeutics such as complement blockade remains to be seen. Further studies exploring these yet-unanswered questions will be needed to guide integration of u-sCD163 into clinical decision making.

New biomarkers related to the diagnosis and treatment of IgAN are emerging, and the knowledge base of novel therapeutic drugs is continuously expanding. Undoubtedly, these biomarkers will play an important role in optimizing treatment decisions and prognostication as our IgAN toolkit continues to grow. Further work exploring validation and integration of these novel biomarkers into clinical care is needed to help us improve the outcomes of IgAN patients.

DISCLOSURE

GL is a scientific advisor to AstraZeneca. The other author declared no competing interests.

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