How Should Pathology Findings Influence Treatment in IgA Nephropathy?

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The Oxford classification of IgA nephropathy is widely adopted, and numerous studies have addressed its value. Although most publications have found associations between each of the MEST-C lesions with progressive disease, only the tubulointerstitial score has consistently and independently predicted kidney outcomes.[1] Many studies report an immunosuppression bias, with some finding that glucocorticoids modify the predictive values of the E, S, and C lesions. A prespecified analysis in the TESTING trial addressed the effect of methylprednisolone in E0 compared with E1 but failed to reveal a significant interaction, although the analysis was underpowered given the premature data review mandated by safety concerns related to corticosteroid dose.[2] Similarly, a *post hoc* review of the STOP-IgA study did not find an impact of pathology on the response to immunosuppression, but again too few events had occurred and less than half of the subjects had available pathology slides for Oxford scoring.[3] Given inconsistencies from retrospective studies and the absence of confirmatory findings from prospective trials, the recent 2021 Kidney Disease: Improving Global Outcomes Glomerular Disease Guidelines state "that there is insufficient evidence to support the use of the Oxford classification in determining when any glucocorticoid therapy should be commenced."[4]

Ideally, answering how biopsy findings should influence treatments would require a randomized controlled trial with a prespecified pathology-related hypothesis. Pragmatically, defining such as question is difficult because many permutations of the MEST-C score exist, and performing a separate study in each state would be impossible. Furthermore, the time from the kidney biopsy to randomization would need to be short, which has not been the case in previous trials largely related to barriers to recruitment (Table 1). Hence, we still rely on large observational cohorts to suggest how pathology and immunosuppression should be addressed using a simple experimental design.

Itami *et al.*[5] endeavored to answer this question by studying a retrospective cohort of 858 patients from Japan. The authors first performed propensity-adjusted analyses within each possible score of the MEST-C classification and found that glucocorticoids were significantly associated with a reduced risk of end-stage kidney disease only in the presence of M1, E1, S1, or C1–2 lesions. Unlike previous studies considering only the binary presence or absence of lesions, the number of lesions was summed to create a "steroid responder score" of 0 to 4. They also determined that the presence of T1–2 was associated with a lack of response to glucocorticoids, as opposed to T0 and similarly defined the T lesion as the "steroid non-responder score." They then reanalyzed the benefits of glucocorticoid therapy according to 6 possible permutations defined by low (0), medium (1–2), or high (3–4) active lesions, each with or without significant interstitial tubular atrophy of interstitial fibrosis. In those with a "low" active lesion score, few progressed to end-stage kidney disease regardless of the T status, supporting conservative management only. Those with 1–2/4 active lesions and significant tubulointerstitial scarring had no benefits using corticosteroids with hazard ratios ∼1.0 using different models. By contrast, the use of glucocorticoids was associated with a reduced hazard (0.3–0.5) of end-stage kidney disease in individuals with high activity and

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Table 1. Pathology findings of STOP-IgA, TESTING, and a 2009 publication from Lv *et al.*[6]

Study %	M1	E1	S1	T1−2	C1−2	Median time biopsy to randomization
Lv *et al.*, 2009[a]	77	55	73	30	57	Unknown. All biopsies within 1 yr
TESTING, 2017	58	28	70	61	55	139 d (IQR: 107–244)
STOP-IgA, 2015	26	17	91	41	31	9.4 mo, 6% of biopsies >3 yrs

IQR, interquartile range.
[a]Supplementary data provided by Prof. Hong Zhang of the Peking Institute of Nephrology.

T1−2 or those with medium activity and T0. Finally, those with high activity and little chronicity experienced a remarkable reduction in the risk of end-stage kidney disease using immunosuppression. Validation of their findings could easily be attempted using large existing databases, perhaps excluding those with a significant time lag between the kidney biopsy and the initiation of immunosuppression. Taken together, the conclusions from the Japanese cohort suggest that the pre-specified question to test is whether glucocorticoids are effective when the kidney biopsy results reveal either high activity as defined previously or medium activity combined with little tubular atrophy or interstitial fibrosis. The 2021 Kidney Disease: Improving Global Outcomes guidelines also caution against use of immunosuppression when the estimated glomerular filtration rate is <30 ml/min per 1.73 m^2 in the absence of a rapidly progressive glomerulonephritis.

Could these results also explain divergences between conclusions from STOP-IgA and other randomized trials? The MEST-C scores are available for STOP-IgA,[3] TESTING,[2] and a 2009 publication from Lv *et al.*[6] All 3 controlled studies had optimal conservative treatment, and the pathology findings are found in Table 1. Although we cannot derive the exact activity scores from the reported percentages of each MEST-C lesion, they seem lower in STOP-IgA, which could partly explain the lack of benefits from

immunosuppression in that cohort. It is also possible that these lesions had significantly changed from biopsy to randomization with greater chronic and fewer active lesions.

The proposed distinction between active and chronic lesions is not new and has long been used in lupus nephritis. The 2018 revision of the Renal Pathology Society classification for lupus nephritis clarified and modified the activity and chronicity scores.[7] Notably, segmental glomerulosclerosis is included in the chronicity index for lupus nephritis given its association with renal failure,[8] whereas in the Itami study in IgA nephropathy, it may indicate responsiveness to immunosuppression. At face value, this may suggest that segmental glomerulosclerosis has different implications in different diseases. Nevertheless, it is possible that this reflects the spectrum of lesions that may be interpreted as segmental sclerosis. As much as focal and segmental glomerulosclerosis encompasses different diseases, the Oxford S score incorporates multiple lesions. An analysis of a subset of the original Oxford cohort detailed these, including hyalinosis, segmental sclerosis, adhesions, podocyte hypertrophy, and tip lesions.[9] The presence of podocyte hypertrophy or tip lesions was associated with much higher proteinuria and linked to a worse prognosis without immunosuppressive treatment but a favorable one when treated, supporting the designation of these as active lesions. Furthermore, segmental sclerosis or hyalinosis

without adhesions or podocytopathic features was not associated with proteinuria and seemed to reflect chronicity.[9] Hence, a refinement of the S score may be necessary.

There are additional hurdles to address with the MEST-C classification. The most important relates to its reproducibility. An analysis of the European VALIGA cohort identified marked differences between local and central (Oxford) assessments of the MEST-C score.[10] These disagreements were not random. Mismatches in the M and E scores carried different associations with progression when only local pathologists found the lesions instead of *vice versa*. Although reproducibility may be disappointing, the Oxford classification methodology has allowed to characterize the problem, offering the possibility to correct assessments and standardize reporting. This enables stakeholders to speak the same language and promote uniform research and clinical approaches.

Despite the ongoing uncertainty on how pathology should influence treatment, it is precisely the same M, E, S, and C scores identified by the Itami study that were independently associated with the decision to administer glucocorticoids in the VALIGA cohort, along with age and proteinuria.[10] These lesions had a greater impact on treatment allocation than the estimated glomerular filtration rate or tubulointerstitial lesions suggesting European nephrologists considered activity and chronicity in IgA nephropathy akin to lupus nephritis long before the recent Japanese publication. Pathology findings holds great predictive value compared with a single cross-sectional clinical assessment (proteinuria, estimated glomerular filtration rate, blood pressure), but repeated clinical assessments eventually outweigh the findings

of a single biopsy.[11] If the conclusions from the Japanese cohort are validated, this would strongly support the inclusion of a simple prespecified pathology-defined hypothesis in future trials. It would also encourage repeating renal biopsies in individuals who deteriorate long after their initial biopsy, personalizing the allocation of potentially hazardous treatments, and ultimately improving patient outcomes.

DISCLOSURE

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