PATHOLOGY OVERVIEW

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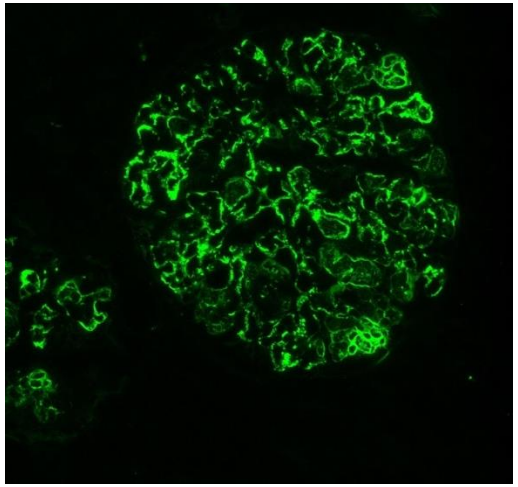
DISCLOSURES

- Consultancy fees from Novartis, Sobi and Q32Bio. Lecture fees from Sobi

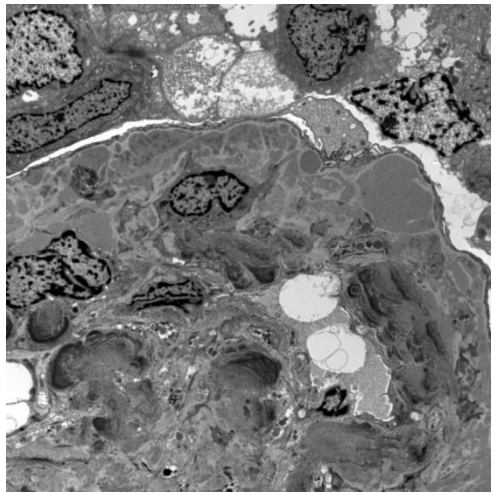
C3 glomerulopathy

- Biopsy is essential for diagnosis

- C3 glomerulopathy
  - Glomerulonephritis due to abnormal control of complement activation, deposition or degradation.
  - Glomerular C3 fragments in the absence of immunoglobulins and components of the classical pathway
  - Electron dense deposits on EM



C3c



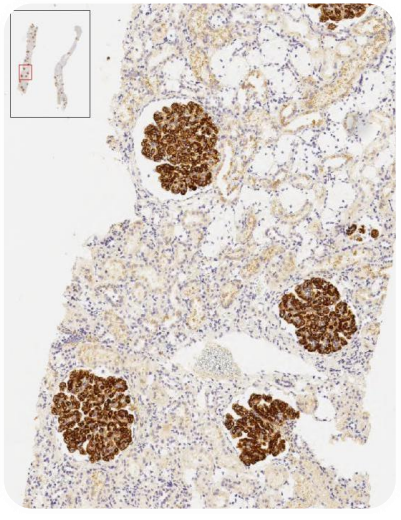
Problems with C3G diagnosis

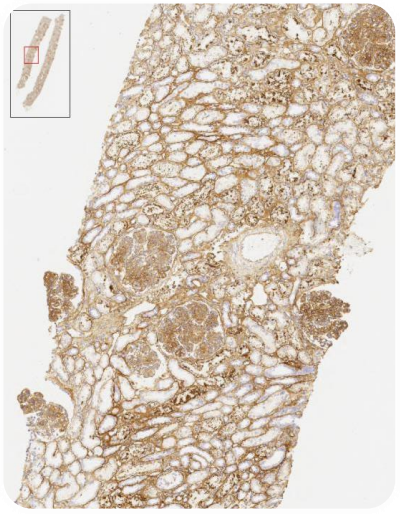
- Immunoglobulin is often present in small amounts.
- Consensus opinion is the best criterion is **dominant C3** staining with the intensity of C3 staining **at least two orders of intensity stronger** than any combination of IgG, IgM, IgA, and C1q
- This is not a definition but just an aid for diagnosis
- This criterion will capture 88% of cases of DDD but possibly fewer cases of C3 GN, based on studies performed at one centre
- Criteria were validated in cases using immunofluorescence for C3c on frozen sections

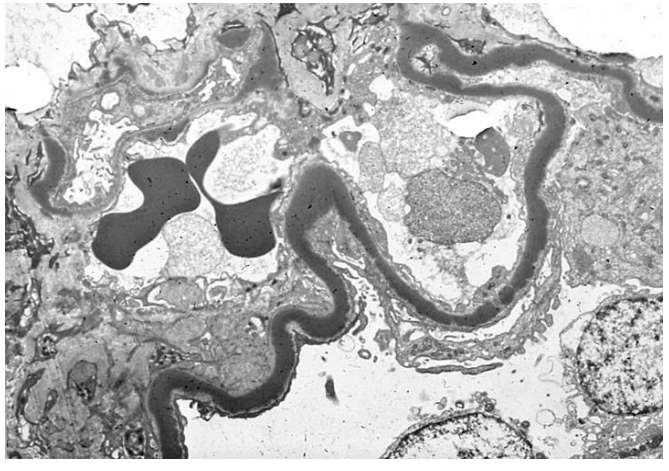
Problems with C3G diagnosis

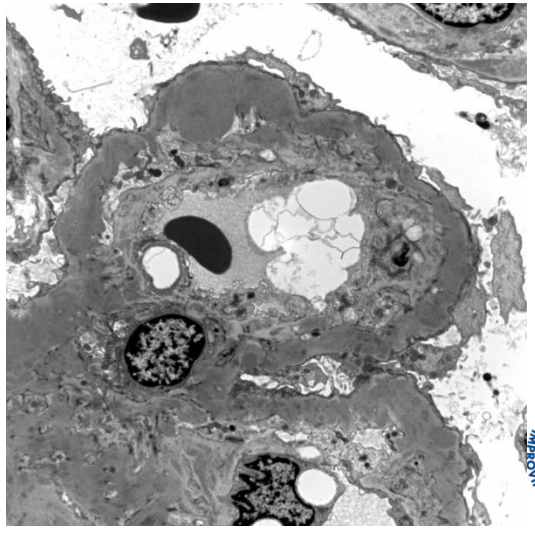
In real life, interpretation will also need to take into account:

- The method by which C3 is detected (frozen tissue vs paraffin embedded tissue)
- Electron microscopy (typical C3G features)
- Clinical history
- Complement serology and genetics



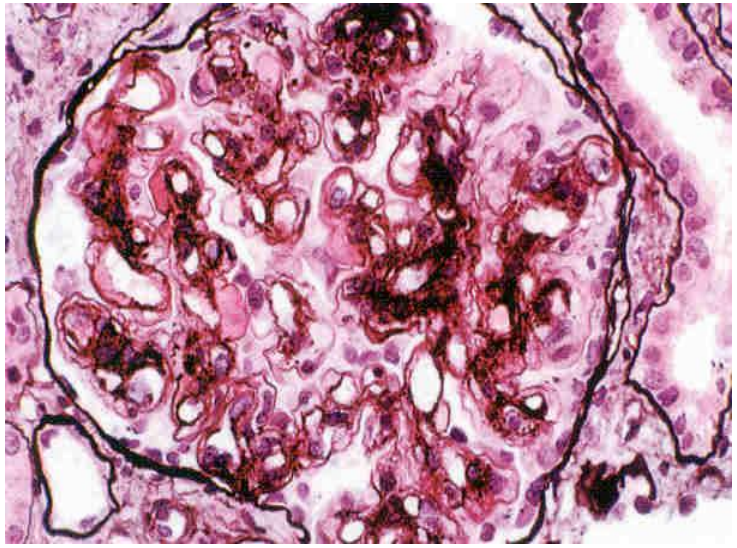


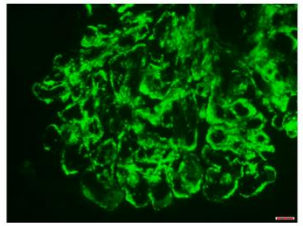




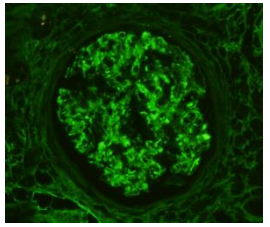
Idiopathic immunoglobulin-associated MPGN

- **MPGN pattern** of injury on light microscopy
- C3 and immunoglobulins present – **does not fulfill criteria for C3-dominant** GN
- **No evidence of secondary cause** – exclude autoimmunity, infection, monoclonal immunoglobulin deposition (pathologist needs to exclude 'masked' monoclonal immunoglobulin deposition with protease digestion)





C3c



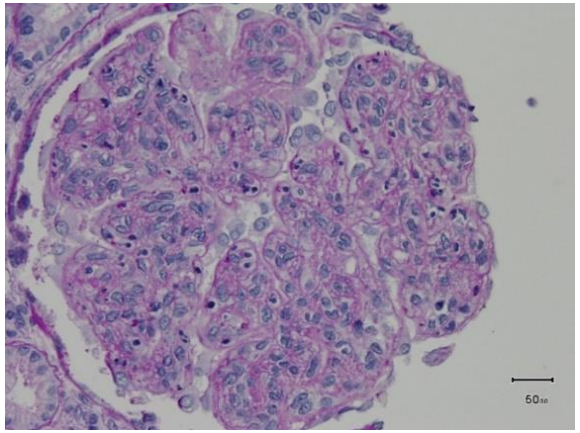
IgG

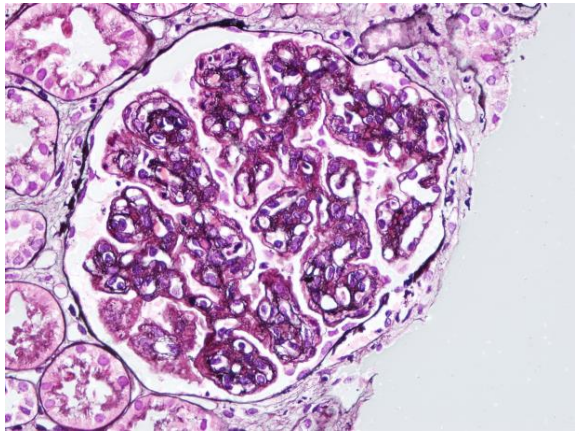
Idiopathic immunoglobulin-associated MPGN

- What is the evidence Ig-MPGN is complement mediated?
- Similar incidence of low C3, nefs and genetic variants as in C3G (e.g. Iatropoulos Mol. Immunol. 2016)
- Transition of Ig-MPGN to C3G in later biopsies
- Response to C3 inhibition (VALIANT trial)
- However, there is no consensus recommendation for how much C3 staining should be present
  - Some authors have assumed C3 is dominant or co-dominant
  - Iatropoulos – MPGN cases had mean C3 intensity of 2.61
  - In VALIANT trial of pegcetacoplan Ig-MPGN cases had C3c intensity of at least 2+
  - Should minimum criteria for C3 staining be added to diagnostic criteria?

C3G and Ig-MPGN – how does pathology relate to clinical features and outcome

- At presentation proteinuria correlates with endocapillary hypercellularity and double contours (Lomax-Browne CJASN 2022)
- This is important as these features may respond at different rates to treatment. Inflammation may respond quickly while repair of capillary wall may take months to years.
- This is supported by APPEAR-C3G study where the only change in the activity score features at 6 months was endocapillary hypercellularity with no change in double contours
- At presentation eGFR is negatively associated with cellular crescents, interstitial inflammation and interstitial fibrosis/tubular atrophy

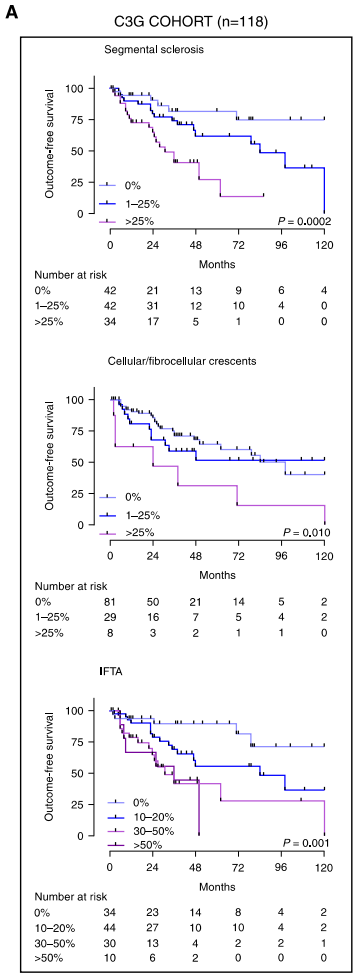




C3G and Ig-MPGN – how does pathology relate to outcome

Histological features at time of presentation and clinical outcome

- All studies agree that tubular atrophy/interstitial fibrosis is best predictor of poor outcome
- Other features predictive in some studies are glomerulosclerosis, cellular/fibrocellular crescents and arteriosclerosis

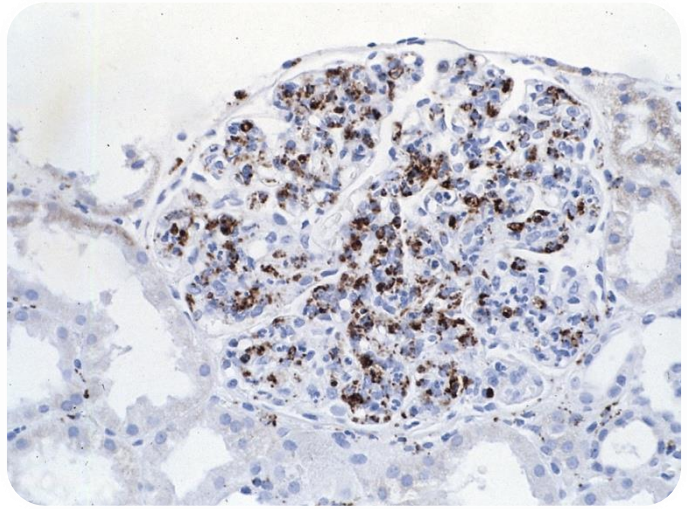


C3GN n=101, DDD n=17

C3G and IC-MPGN – what other information might we get from the biopsy?

- Can we analyse the biopsy in other ways that are more informative?
  - Immunohistochemistry for CD68 to quantitate inflammation
  - This is a reliable and objective way to quantitate endocapillary inflammation and should be routine in further studies

  - Standardization of C3 staining methods and quantitation
  - Staining of more complement components- C3c, C3d, FB, C5b-9 etc. No evidence at present that this is useful



CD68

C3G and IC-MPGN – what other information might we get from the biopsy?

- Can biopsy features predict response to treatment with complement blockers?

- This information could be assessed in published trials with further analysis, and in future treated patients

C3G and Ig-MPGN. Role of repeat biopsy

- What do we know?

  - C3 inhibition can lead to loss of C3 staining – in VALIANT trial 71% of patients had no C3c staining at 6 months (It would be interesting to know what was different about these patients)

  - Factor B inhibition led to reduction in glomerular inflammation at 6 months in the APPEAR-C3 trial with no change in capillary wall double contours

C3G and Ig-MPGN. Role of repeat biopsy

- There may be several reasons why proteinuria could persist after complement blockade
  - Persistent C3 deposition
  - Persistent glomerular inflammation
  - Slow resolution of capillary wall structural changes
  - Adaptive haemodynamic changes secondary to scarring

- Repeat biopsy in treated patients with persistent proteinuria will allow assessment of whether there is resolution of C3 deposition and the likely cause of proteinuria

C3G and Ig-MPGN - transplant recurrence

- Recurrence is common. C3c 67-89%; IG-MPGN 15-45%.
  - Variability reflects:
    - Protocol biopsies vs biopsies for cause
    - Histological vs clinical recurrence
    - Variability of definitions in historical series particularly for MPGN

- In a series including protocol biopsies, histological recurrence of C3G seen in 89% at 33 (13, 141) days after transplantation (Tarragon CJASN 2024)
  - 19% normal glomerular cellularity, 75% mesangial h/c. one endocapillary h/c
  - Half of patients progressed to endocapillary h/c or MPGN at one year
  - Only 30% had proteinuria >300mg/g at first biopsy showing recurrence

C3G and Ig-MPGN - transplant recurrence

- Recurrence of C3 deposition is common and occurs early
- At the time of immunofluorescent recurrence there may be little glomerular inflammation and only low-grade proteinuria
- How should histological recurrence be defined?
  - Standard IF criteria (C3c at least 2+)
  - C3c at least 1+ together with electron dense deposits?
  - C3 deposition **and** evidence of activity (endocapillary h/c or double contours)?
- Should protocol biopsies be performed – if so, when?
- When should specific complement inhibiting treatment be started? Histological or clinical recurrence?
- Should the approach be different if there has been recurrence in a previous transplant?

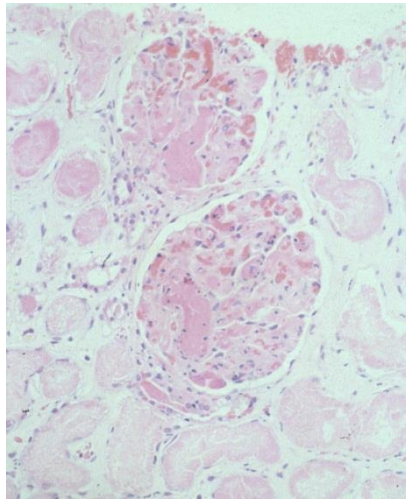
C3G and Ig-MPGN - transplant recurrence

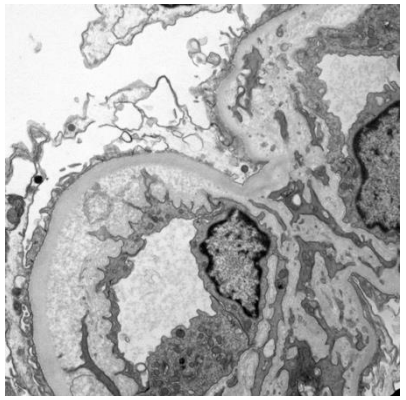
- I think we are unlikely to see trials that will answer these questions
- More natural history studies (particularly for Ig-MPGN) would be useful
- Need to gain as much information as possible from real-life experience of treatment of transplant patients with complement inhibiting drugs. Ideally the examination of biopsies in these patients should be standardized
  - IF – antibodies used and quantitation
  - EM
  - Light microscopic features – assessment and quantitation
  - CD68 staining

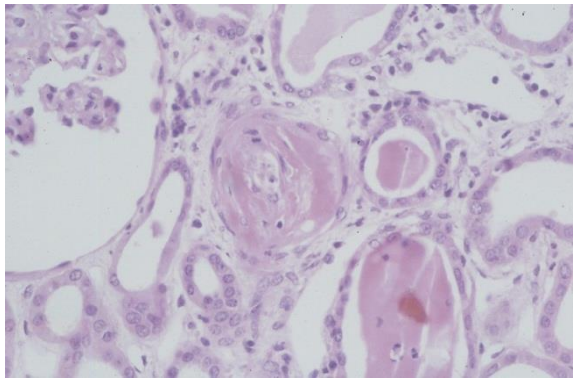
Thrombotic microangiopathy (TMA)

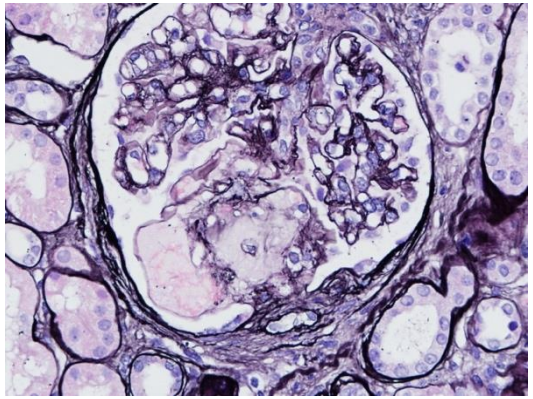
- Endothelial injury leading to characteristic lesions in glomeruli, arterioles and arteries in the kidney and other organs. Often, but not always, thrombosis is present.
- If the endothelial injury and fibrin deposition is severe they lead to haemolysis with red cell damage (microangiopathic haemolytic anaemia)
- In many cases the diagnosis is made without kidney biopsy

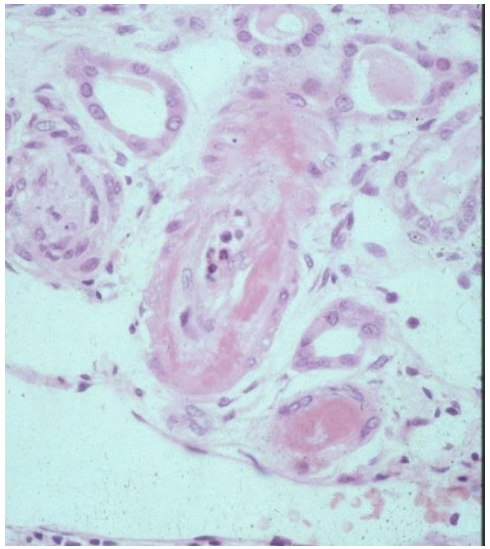
TMA

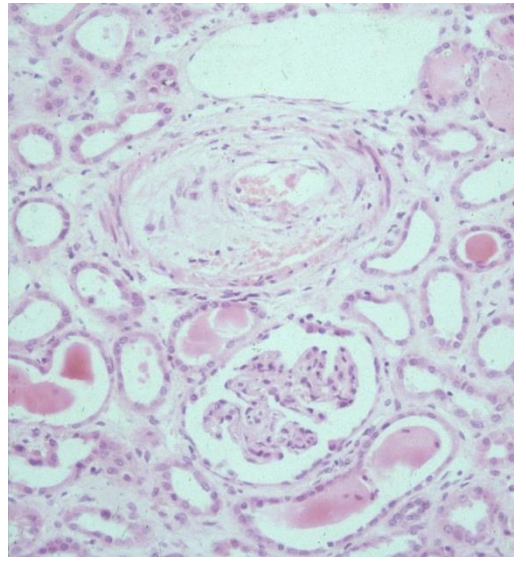












TMA – kidney biopsy

- Acute changes may be slow to resolve after treatment and kidney biopsy is clearly helpful in showing the extent of irreversible chronic damage
- Can the kidney biopsy help in determining the cause of endothelial injury?
  - In 2015 at the KDIGO controversies meeting I said:
  - Shiga toxin associated HUS shows predominant glomerular involvement
  - TTP has platelet rich thrombi
  - TMA due to malignant hypertension shows predominant vascular involvement
- What can we add now?

TMA

- A very important practical question is whether TMA in the context of severe ("malignant") hypertension is solely due to hypertension injuring the endothelium or is due to complement-mediated endothelial injury with subsequent hypertension.
- My understanding of the literature is that:
  - Severe hypertension with retinopathy is common in complement-mediated TMA
  - Primary severe hypertension rarely leads to microangiopathy severe enough to cause microangiopathic hemolysis
  - If the only lesion seen on biopsy in severe hypertension is myxoid arterial intimal thickening it is very unlikely the TMA is complement-mediated
  - If glomerular and arteriolar thrombi are present, then TMA is much more likely to be complement-mediated than due to hypertension

TMA

- Can complement immunohistochemistry help to define the cause

- Endothelial injury due to any cause will lead to activation of the alternative pathway with subsequent deposition of C5b-9

Overall, I am not convinced that detecting complement components in the biopsy adds useful diagnostic information

TMA without haematological features

- Endothelial injury leading to characteristic lesions in glomeruli, arterioles and arteries in the kidney and other organs. Often, but not always, thrombosis is present.
- If the endothelial injury and fibrin deposition is severe they lead to haemolysis with red cell damage (microangiopathic haemolytic anaemia)
- In many cases the diagnosis is made without kidney biopsy
- However, if the lesions are not severe enough to lead to haemolysis then the diagnosis will only be made on renal biopsy
- This has been called ‘Renal-limited TMA’

TMA without haematological features

- Maisons et al (KI 2024) identified 757 patients with kidney biopsies showing TMA
- 45% had no haematologic features (RL-TMA)
- Patients with RL-TMA had lower creatinine levels (median 184 vs 346 mmol/L)
- RL-TMA resulted from virtually all known causes of TMA and included 25% of the patients with complement-mediated TMA
- The study shows that in many patients with TMA (including complement-mediated TMA) diagnosis will only be made on kidney biopsy
- Paradoxically, in the paper, they refer to many of the patients with TMA without haemolysis as having atypical haemolytic-uraemic syndrome underlining the need to consider revision of nomenclature

			Individual components Mean (SD)		Iptacopan 200 mg b.i.d. vs Placebo	
Parameter*	**Treatment**	**N/n**	**Baseline**	**Change from baseline**	**Adjusted mean difference**	**Nominal 1-sided p-value**
Endocapillary proliferation	Iptacopan	37/33	1·9 (1·07)	-1·0 (1·07)	-0·443	0·0240
	Placebo	36/34	1·6 (1·07)	-0·4 (0·99)		
Leukocyte infiltration	Iptacopan	37/33	1·8 (1·06)	-1·0 (1·00)	-0·461	0·0199
	Placebo	36/34	1·6 (1·08)	-0·4 (1·05)		
Interstitial inflammation	Iptacopan	37/33	0·2 (0·46)	-0·2 (0·36)	0·013	0·7030
	Placebo	36/34	0·1 (0·29)	-0·1 (0·29)		
Mesangial hypercellularity	Iptacopan	37/33	2·9 (0·24)	0·0 (0·25)	0·073	0·7942
	Placebo	36/34	2·8 (0·41)	0·1 (0·60)		
Membranoproliferative morphology	Iptacopan	37/33	2·9 (0·24)	0·0 (0·25)	0·027	0·6270
	Placebo	36/34	2·8 (0·48)	0·1 (0·57)		
Crescent formation	Iptacopan	37/33	0·1 (0·42)	-0·1 (0·42)	-0·029	0·1681
	Placebo	36/34	0·1 (0·34)	0·0 (0·39)		