TUESDAY CONFERENCE

2/19/2013
62 yo AA male, hx of hep C, CAD admitted for chest pain, was consulted for microscopic hematuria, and protienuria, with increased Cr from normal baseline.

ROS: negative for fever, rash, weight loss, joint pain, visible hematuria, dysuria, abdominal pain, vision impairment.

FH: NC.
PMH: hep C diagnosed 1983 (was said due to blood transfusion), DM (well controlled), CAD S/P CABG in 2007, HTN.

Home meds: amlodipine, atorvastatin, nitrate, insulin, aspisin, plavix, metoprolol, hydralazine.

Allergy: unknown

Social: no alcohol, tobacco, or illicit drugs.
Gen: no acute stress.
neck: no bruite, LAD, or JVD.
chest: clear
CV: regular, no GMR
Abdomen: NT, obese.
Ext: 1+ edema, no rash
normal joints ROM
<table>
<thead>
<tr>
<th>Date</th>
<th>Cr</th>
<th>BUN</th>
<th>Na</th>
<th>k</th>
<th>CO2</th>
<th>Alb/cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/9/12</td>
<td>0.9</td>
<td>18</td>
<td>142</td>
<td>4.6</td>
<td>26</td>
<td>400 mg/g</td>
</tr>
<tr>
<td>1/7/13</td>
<td>1.3</td>
<td>28</td>
<td>139</td>
<td>5</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2/5/13</td>
<td>1.9</td>
<td>30</td>
<td>138</td>
<td>5.2</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>2/11/13</td>
<td>2.1</td>
<td>35</td>
<td>139</td>
<td>5.1</td>
<td>24</td>
<td>500</td>
</tr>
</tbody>
</table>
- H/H: 10/30, WBC: 4.9, Plt: 266
- UA: protein > 300, RBC: 30-40, WBC: 10
- INR: 0.9, Alb: 3.7, LFTs: WNL
- RF: 431 (0-39)
- HCV RNA: 1400000
- C4 > 5, C3: 145
- Cryo: N?
- Renal US.
53 yo AA male presents
Pathophysiology of MPGN.

Normal Glomerular Capillary Wall and Immune-Complex–Mediated Membranoproliferative Glomerulonephritis (MPGN).

Membranoproliferative GN (MPGN) is a pattern of injury rather than a specific disease, characterized morphologically by mesangial proliferation and expansion, lobularization of the glomerular tufts, and double contours.

The older classification, based on ultrastructural morphology and location of electron-dense deposits (MPGN type I, type II, type III, etc.), is being replaced with a more modern classification schema based on pathogenetic mechanisms.
MPGN is divided according to its appearance on IF into an Ig+C3+ and C3+ only categories.

A third category, Ig-C3- is largely confined to some cases of chronic thrombotic croangiopathies and de novo chronic transplant glomerulopathy.

Selective depression of C4 is frequently seen in hepatitis C–related MPGN

Possible mechanisms by which factor H limits injury in immune complex glomerulonephritis.
Clinical presentation:

- Mostly mild proteinuria and microscopic hematuria.
- Rapid deterioration of renal function in 25% of patients.
- 50% have moderate renal failure and 80% have hypertension.
- A clinical regression is observed in 10 – 15% of patients with nephritic syndrome.
- In 30% of the cases, the clinical course is slow, and renal function is maintained for many years.
- In about 20% of the patients, the disease is characterized by episodes of acute relapse with nephrotic syndrome.
- In the long term, less than 15% of patients with MC-related nephropathy may progress towards ESRD requiring dialysis.
- An increased risk of end-stage renal disease is associated with age, severity of renal failure at diagnosis, splenomegaly, purpura and hypocomplementemia.
The association of HCV infection and idiopathic MPGN (in the absence of cryoglobulinemia) is controversial.

Laboratory tests that suggest the presence of a cryoglobulin are a positive RF together with low C4 levels, particularly in patients with MPGN on Bx. In some patients, immune deposits with ultrastructural features compatible with cryoglobulins can be detected on biopsy of affected tissue, such as the kidney or skin.
optimal treatment is very problematical and highly uncertain due to its extreme pathogenetic heterogeneity, treatment must be based on the underlying pathogenetic mechanisms.

- Treatment should take into account the age of the patient, severity of the concomitant liver disease, and extent of renal involvement.

- When extensive crescents are present, an aggressive regimen of pulse steroids and immunosuppressive agents can yield good results, but controlled trials are lacking and the details of the most effective and safe regimens for this lesion are still largely unknown.
Recommendations for the management of MCS in hepatitis C virus-infected patients

- aim of treatment to prevent irreversible organ damage, reducing pain and improving the patients' quality of life.
- However, the treatment is still largely empirical. Any rational therapeutic approach should have three main objectives to:
  - eradicate HCV
  - to limit or suppress B lymphocyte proliferation.
  - and to treat the vasculitis and reduce the damage caused by circulating immune complexes

Autoimmunity Reviews 10 (2011) 444-454
Methods:

- Specific key words and MeSh terms were selected in MEDLINE and variously combined to search for papers concerning the Treatment of patients aged more than 18 years with HCV-related MCS available in MEDLINE, EMBASE and Cochrane Central. The search was restricted to papers written in English, French and Italian.
The selected papers included randomised controlled trials (RCTs), observational studies (prospective and retrospective cohort and case-control studies), and case series of at least three patients.
Levels of evidence (Oxford, May 2001, http://www.cebm.net) of each study were assessed and classified from:

- level 1a (a systematic review of RCTs) to level 4 (case series), with level 5 being used for expert opinions.

- The strength of the experts' recommendations was classified from A (consistent level 1 studies) to D (inconsistent or inconclusive studies at any level)
1. **Antiviral therapy:**
   - Studies are difficult to compare because of the heterogeneity of treatment regimens, patient selection, response evaluations, and follow-up.
   - They all had poor statistical power because of their small sample sizes.
   - The presence of cryoglobulinemia did not affect the response to IFN in patients with chronic HCV infection.
It is also worth noting that the regression of peripheral blood and bone marrow monoclonal B lymphocytes was observed in the MCS patients who cleared HCV as a result of IFN therapy.

pegylated IFN (Peg-IFN) α-2a and α-2b, which have prolonged bioavailability and greater antiviral efficacy than standard IFN
Peg-IFN combined with ribavirin is now the standard of care for HCV treatment and leads to 41–54% sustained viral responses (SVRs) in the case of genotype 1, and approximately 80% in the case of genotypes 2 and 3.

There are only two pilot studies of the treatment of MCS with PegIFN+RBV.
Mazzaro et al, and Cacoub et al:
The treatment was found to be safe and well tolerated in both of these studies, which demonstrated that in HCV-associated MCS combined Peg-IFN+RBV therapy leads to a SVR rate similar to that of HCV-infected patients without MCS, and strongly suggested this combination as the first-line treatment for MCS patients.

Statements

- HCV RNA suppression is associated with an improvement or the disappearance of the clinical and laboratory manifestations of HCV-related (MCS). The achievement of a (SVR) leads to a complete recovery from all signs and symptoms of disease in the majority of patients (3b C).
- In patients with HCV infection, the presence of MCS does not substantially affect the rate of SVRs to combined pegylated interferon and ribavirin therapy (4 C).
- An attempt at viral eradication should be considered a first-line therapeutic option in patients with mild–moderate HCV-related MCS in the absence of any major contraindication (4 C).
- An extended duration of treatment (up to 48 weeks for HCV genotypes 2 or 3 and 72 weeks for HCV genotypes 1 or 4) may be considered in the case of virological non-responders who show clinical and laboratory improvements in MCS (5 D).
direct-acting antiviral (DAA) agents
Selected Baseline Characteristics of Patients Who Received at Least One Dose of Study Medication, According to Cohort and Treatment Group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonblack Cohort</th>
<th>Black Cohort</th>
<th>Both Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (N=311)</td>
<td>Group 2 (N=316)</td>
<td>Group 3 (N=311)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>48±10</td>
<td>49±9</td>
<td>51±9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>171 (55)</td>
<td>200 (63)</td>
<td>188 (60)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td>296 (95)</td>
<td>304 (96)</td>
<td>295 (93)</td>
</tr>
<tr>
<td>White</td>
<td>296 (95)</td>
<td>304 (96)</td>
<td>295 (93)</td>
</tr>
<tr>
<td>Black</td>
<td>52 (100)</td>
<td>52 (100)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>Asian</td>
<td>9 (3)</td>
<td>4 (1)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2)</td>
<td>8 (3)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td>203 (65)</td>
<td>226 (72)</td>
<td>218 (70)</td>
</tr>
<tr>
<td>North America</td>
<td>203 (65)</td>
<td>226 (72)</td>
<td>218 (70)</td>
</tr>
<tr>
<td>Europe</td>
<td>98 (32)</td>
<td>78 (25)</td>
<td>83 (27)</td>
</tr>
<tr>
<td>Latin America</td>
<td>10 (3)</td>
<td>12 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>79±16</td>
<td>82±17</td>
<td>80±17</td>
</tr>
<tr>
<td>HCV subtype — no. (%)‡</td>
<td>186 (60)</td>
<td>195 (62)</td>
<td>197 (63)</td>
</tr>
<tr>
<td>1a</td>
<td>186 (60)</td>
<td>195 (62)</td>
<td>197 (63)</td>
</tr>
<tr>
<td>1b</td>
<td>112 (36)</td>
<td>111 (35)</td>
<td>104 (33)</td>
</tr>
<tr>
<td>Missing data</td>
<td>13 (4)</td>
<td>10 (3)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>HCV RNA level — no. (%)</td>
<td>285 (92)</td>
<td>287 (91)</td>
<td>288 (93)</td>
</tr>
<tr>
<td>&gt;400,000 IU/ml</td>
<td>285 (92)</td>
<td>287 (91)</td>
<td>288 (93)</td>
</tr>
<tr>
<td>&gt;800,000 IU/ml</td>
<td>258 (83)</td>
<td>268 (85)</td>
<td>262 (84)</td>
</tr>
<tr>
<td>Metavir fibrosis score — no. (%)§</td>
<td>277 (89)</td>
<td>279 (88)</td>
<td>265 (85)</td>
</tr>
<tr>
<td>0, 1, or 2</td>
<td>277 (89)</td>
<td>279 (88)</td>
<td>265 (85)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>23 (7)</td>
<td>26 (8)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Missing data</td>
<td>11 (4)</td>
<td>11 (3)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Steatosis — no. (%)§</td>
<td>192 (62)</td>
<td>213 (67)</td>
<td>208 (67)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Boceprevir was given for 24 weeks in group 2 and for 44 weeks in group 3, irrespective of the rapidity of achievement of an undetectable HCV RNA level. See Table S1 in the Supplementary Appendix for a complete list of baseline characteristics.

† Race was self-reported. Hispanic or Latino was given as a second self-identification by 8 to 13% of the patients in each treatment group in the nonblack cohort and in one patient in the black cohort.

‡ The HCV subtype was ascertained by sequencing of the nonstructural 5B region.

§ Metavir scores and steatosis were determined on the basis of assessment of liver-biopsy specimens by a single pathologist who was unaware of the assignment to the boceprevir or placebo group. Possible fibrosis scores are as follows: 0 (indicating no fibrosis), 1 (indicating portal fibrosis without septa), 2 (indicating portal fibrosis with few septa), 3 (indicating numerous septa without cirrhosis), and 4 (indicating cirrhosis). Steatosis was analyzed as being present or absent.

Study Design.

### Table 4. Odds Ratios for a Sustained Virologic Response, According to Predictor Variables.*

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3 vs. group 1</td>
<td>3.5 (2.6–4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 2 vs. group 1</td>
<td>3.1 (2.3–4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black cohort vs. nonblack cohort§</td>
<td>0.5 (0.3–0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline HCV RNA level ≤400,000 vs. &gt;400,000 IU/ml</td>
<td>3.9 (2.1–7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≤40 vs. &gt;40 yr</td>
<td>1.5 (1.0–2.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>No cirrhosis vs. cirrhosis</td>
<td>2.5 (1.4–4.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Statin use vs. no statin use</td>
<td>3.4 (1.1–10.7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* The odds ratios were estimated in a multivariate stepwise logistic-regression model that included baseline predictors of sustained virologic response in all treated patients (in the black and nonblack cohorts combined). CI denotes confidence interval.

† Only covariates remaining significant at an alpha level of 0.05 after adjustment for the other variables were retained in the model and are listed in the table. Factors entered but not retained in the model were region, sex, age, weight, body-mass index, hepatitis C virus (HCV) genotype 1 subtype as ascertained by means of the Trugene assay, hepatic steatosis, platelet count, alanine aminotransferase level, and Metavir fibrosis score at baseline. In an expanded model that included response data during the treatment period, an HCV RNA level at week 4 that was undetectable or that had decreased by 1 log_{10} IU per milliliter or more from baseline (vs. a decrease of <1 log_{10} IU per milliliter) had the highest odds ratio: 9.0 (95% CI, 6.3 to 12.8; P<0.001).

‡ P values were calculated with the use of the chi-square test.

§ Race was self-reported.
Recommendations:

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin (Class 1, Level A).

2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin (Class 1, Level A).

AASLD practice guidelines 2011
IL28B genotype is a robust pretreatment predictor of SVR to peginterferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with genotype 1 chronic hepatitis C virus infection.

Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment duration needed (Class 2a, Level B).

AASLD practice guidelines 2011
Biological therapy:

- none of these studies was designed to define the best first-line treatment in MCS and the advantages of combined therapy versus RTX monotherapy have never been investigated up to now in randomised trials.
- Rituximab (RTX) is the only biological therapy that has proved to be beneficial in MCS, and should be considered when treating patients with severe clinical manifestations such as glomerulonephritis, skin ulcers or peripheral neuropathy (3 C).
- In the same clinical situations, RTX should be preferred over other more conventional treatments such as glucocorticoids, immunosuppressants or apheresis (3 C).
- In the same clinical situations, RTX may significantly reduce glucocorticoids administration (3 C).
- HCV viral load and liver function should be carefully monitored.
Steroids:

- High-dose or pulsed glucocorticoid (GC) therapy plays a substantial role in the management of critical patients with renal or neurological complications or serious vasculitic manifestations (4 C).
- The use of low–intermediate GC doses (0.1–0.5 mg/kg/day) has proved ineffective (1b A), but it has been reported that they improve the results of IFN therapy (1b A).
- In the opinion of some experts, short courses (weeks) of low–intermediate GC doses might be considered to control vasculitic flares in patients who do not respond or who are refractory to other treatments (5 D).
- Chronic treatment with low GC doses should be avoided whenever possible and in any case carefully monitored. Alternative therapies (colchicine, a low-antigen-content diet) should be considered for the maintenance treatment of MCS (5 D).
Apheresis: from case reports

Apheresis (usually combined with other treatments) can be used in the case of severe, life-threatening cryoglobulinemic manifestations (4 C), and is the treatment of choice for hyper-viscosity syndrome (5 B).

- Apheresis can be used to treat severe cryoglobulinemic manifestations when other therapies have failed or cannot be used (4 C).
- **CTX:**
  - the use of CTX alone to treat MCS is not recommended. However, its combined use with apheresis can be considered in the case of serious MCS-related conditions, when other therapeutic approaches fail or are contraindicated (4 C).
  - CTX increases plasma HCV RNA levels (4 C) and the effects of CTX on liver function should be strictly monitored.
Response to Eculizumab in a Patient with Membranoproliferative Glomerulonephritis.