Good afternoon. This is a session on lupus and vasculitis. The only new thing you're going to hear about vasculitis in addition to the pathogenesis that you heard from the previous speaker is that for those of you who are Europeans,
Rituximab was approved by the EMA last week for the treatment of relapsing refractory vasculitis.

Balancing efficacy and toxicity of novel treatments for lupus nephritis: EULAR/ERA-EDTA recommendations

Dimitrios T. Boumpas, Athens, Greece
Why lupus nephritis recommendations?

- Kidney is the most frequent severe manifestation in SLE (lifetime risk 40–60%; certain ethnic groups more severely affected)
- Despite advances in the treatment, a significant proportion develops chronic kidney disease; 15–20% will progress to ESRD

Lupus nephritis is an important disease and we need recommendations for the following reasons because the kidney is the most frequent severe manifestation of lupus with a lifetime risk of 40–60%. In certain ethnic groups the situation is worse like in black Americans but also and this is what probably deserves some attention is that despite advances in the treatment, a significant proportion develops chronic kidney disease and close to 20% will progress to ESRD. This is the work from the Milan group from Gabriella Moroni and colleagues showing the survival of lupus nephritis patients from 1950-1980 and you can see here that there is a significant percentage of patients who then reached ESRD.

Slide 5

Challenges in the management of lupus nephritis

- Who should undergo kidney biopsy and how are the results evaluated?
- Are there any blood tests or biomarkers that can accurately predict kidney biopsy results?
- What is the recommended treatment? Does it differ according to the histological class?
- How are severe forms of lupus nephritis treated?
- Is there a ‘target’ of treatment in lupus nephritis?
- How should treatment failures be treated?
- How are patients followed up? Which tests are useful?
- Management of co-morbidities in lupus nephritis

What are the challenges of the practicing rheumatologist or nephrologist in lupus nephritis? Who should undergo kidney biopsy and how are the results evaluated? Are there any blood tests or biomarkers that can accurately predict kidney biopsy results? Rheumatologists do not need biopsies and they are afraid of them. What is the recommended treatment? Does it differ according to the histological class? Does it make a difference? How important is it? We already heard about some of these issues in the previous discussion. How are the severe forms of lupus nephritis being treated? Is there any controversy? Is there a consensus? Is there a difference between patients and so on? Do we have a target in the treatment of lupus nephritis and what should our target be? And why should we reach it? How should we
define treatment failures? How should I know that my patient has not failed and therefore, I need to change therapy? How do we need to follow the patient? Do we follow anti-DNA antibodies or complement every month? How useful are they? Or are there other laboratory tests? Which tests are useful? How do you manage the comorbidities in lupus nephritis? In the past, we used to talk about them as experts because we did not have evidence.

Slide 6

*During the last decade, a number of large observational cohort studies and randomized controlled trials have been published, upon which, recommendations can be based*

Joint EULAR/ERA-EDTA recommendations for the management of adult and paediatric lupus nephritis.

American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis.
*Arthritis Care & Research 64; 5: 797–808 (2012)*

However, during this last decade the number of large observational cohort studies and randomised controlled trial studies were published and for the first time the community could form recommendations. Due to these considerations two groups one in Europe and one in the States decided to develop evidence and expert-based recommendations for adult and paediatric lupus nephritis. This is a European site and one of the important achievements was that the rheumatologists and nephrologists united together with renal pathologists and paediatric nephrologists and rheumatologists to form these guidelines or recommendations rather than were published in the Annals of Rheumatic Disease and almost simultaneously in Arthritis Care & Research. You have seen them so I'm not here to tell you what you can read. I'm here to tell you some points that are very important so you can evaluate some of these points.
So these are the highlights and points to consider.

Slide 8

What are the indications for kidney biopsy in SLE?

- High index of suspicion!
For the first question, what are the indications for kidney biopsy in lupus? This is a graft; there are some people who claim that patients who have normal urine analysis may have some proliferative lesions. Most people like myself believe that these are not clinically significant.

Slide 8/1

What are the indications for kidney biopsy in SLE?

- High index of suspicion!

but in any case what most people will agree with though is that if we have at least 0.5 g of protein together with glomerular haematuria or cellular casts, then the likelihood that you may have proliferative lesions important for treatment is high and you can see that it is up to 60%. Therefore, those patients are the patients that you should refer for biopsy. The ACR has a similar position.

Slide 8/3

What are the indications for kidney biopsy in SLE?

- High index of suspicion!

- Any sign of renal involvement (in particular, reproducible UPCR ≥0.5 especially with glomerular hematuria and/or cellular casts) should be an indication for renal biopsy.
  (Grade C)

- ACR: all patients with clinical evidence of active LV ▶ ↑ Scr, UPCR ≥1.0, or UPCR ≥0.5 and abnormal sediment

Points to consider

- Clinical, serological, or other biomarkers do not accurately predict biopsy findings
- Biopsy should be performed within the first month after disease onset, preferably before the institution of immunosuppressive treatment, unless contraindicated

Clinical serological or other biomarkers do not accurately predict biopsy findings. There is a lot
of discussion about NGAL and other biomarkers of renal involvement, clinically they not very
useful so we should have a high index of suspicion to do the biopsy when in question and the
biopsy should be performed within the first month after disease onset, preferably before the
institution of immunosuppressive treatment unless contraindicated. But you don't wait if the
patient is on immunosuppressive therapy and you have to give it and you don't wait for the
kidney biopsy and within one month similar to vasculitis things do not change significantly.

Slide 9

Pathological assessment of the kidney biopsy

- EULAR & ACR: International Society of Nephrology-
  Renal Pathology Society 2003 classification [class I →
  VI] (Grade: C)

- Pathology report (EULAR & ACR)
  1. Acute glomerular lesions (activity)
  2. Chronic glomerular lesions (chronicity)
  3. Tubulo-interstitial lesions (acute/chronic)
  4. Vascular bed lesions (associated with aPL)
     (Grade: A-C)

How do you assess the pathology of the kidney biopsy? There was a split when we did these
guidelines but in the end there were some people that believe that you always have to use...
So we decided that for the time being with the limitations that we heard about from the first
speaker that this is the best grading system for this and again, you do this new classification,
the International Society of Nephrology and Renal Pathology Society classification but as
already explained, outlined by the previous two speakers, you have to pay special attention
to the vascular bed lesions especially to those associated with anti-phospholipid antibodies
because the prognosis can be worse and this is a recent publication already shown here. So
what's new? We pay more emphasis to the vascular bed lesions, something that we're not
paying as much attention to.

Slide 10
Now, if we have a limited amount of money how could you best use it? You do the usual H&E, you do the PAS or you can do the silver staining. Do you do immunofluorescence? I don't do it if I have typical nephritis but the consensus from the group was that you have to use immunofluorescence and if you can you may use electron microscopy because electron microscopy can give you additional information, especially in cases of mild early proliferative lesions of subendothelial deposits and other information. So this is what we recommend.

Slide 11

**Indications for immunosuppressive treatment**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III–IV or III–IV&lt;sub&gt;AC&lt;/sub&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Mixed class V + III–IV</td>
<td>A</td>
</tr>
<tr>
<td>Class V with nephrotic-range proteinuria</td>
<td>B</td>
</tr>
<tr>
<td>Class V with UPCR &gt;1.0 despite optimal use of RAAS blockers</td>
<td>C</td>
</tr>
</tbody>
</table>

Other indications [EULAR; not graded]

- Class II with UPCR >1.0 (despite RAAS blockers)
- Class I with podocytopathy (minimal change disease)
- Interstitial nephritis

The next question for different types of lupus nephritis what do the data suggest? Who needs immunosuppressive therapy? By that I mean high doses of steroids and cytotoxic therapy. The data, as you can see the grading is high, used for proliferative, for mixed classes 5, 3 and 4 and also class 5 with nephrotic range proteinuria and there is consensus between EULAR and ACR however here we're a little more split. The ACR if the proteinuria is not in the nephrotic range, it does not recommend therapy. We felt at the end of the day that lupus membranous is a little bit different I will get into that and you should consider therapy of proteinuria is more than 1 g and I will come back to this. Other indications, you can see them here. These are details that you can read in the slides when you see them.
As far as the treatment is concerned, as you know, in the treatment of lupus nephritis and vasculitis you have an induction with different regimens and remission, maintenance of remission with azathioprine and MMF.

**Immunosuppressive treatment in class III-IV lupus nephritis**

**NIH regimen**
- High-dose IV-CY
- qm 6 mo for I
- q3m 2 yrs for M
- 50% ovarian failure
- infectious side effects
- no effect on survival

**Euro-Lupus regimen**
- Low-dose IV-CY
- 6 x 500 mg q2w for I
- AZA for M

**ALMS (MMF)**
- MMF for 5 and M7

These are the regimens: the NIH regimen, the Euro-Lupus regimen and the ALMS (MMF) regimen. I would like to remind you that there was a 50% ovarian failure with a high dose of cyclophosphamide used in our NIH protocols.
So if you balance the efficacy with the toxicity, this is what we recommend as initial therapy for induction of lupus nephritis. For proliferative lupus nephritis, we think that the first line of treatment should be mycophenolate. We're targeting a dose of 3g/day for 6 months. This is Grade A, we have very good data. Or low dose IV cyclophosphamide 3 g over 3 months, this is Grade B based on randomised controlled trials and these trials were done by Frederic Houssiau. This is in combination with corticosteroids and this is the initial therapy. How many steroids? 3 pulses of IV methylprednisolone for 3 days. Then oral prednisone but no more than 0.5 mg/kg for the first 4 weeks and then tapered to less than 10 mg /day by 4-6 months. Why did we decide to suggest MMF and not cyclophosphamide? This is not because it's more efficacious but just because of the consensus of ovarian toxicity which with a high dose of cyclophosphamide can be significant. So it's assessing the benefits to the risk and toxicity ratio, that's the only combination and the reason for that and I'll come back to that.

Slide 15

Recommendations for initial (induction) treatment of class III-IV LN

- For patients with class III, or IV + C1 (±V) and class IV, or IV + C (±V) LN, mycophenoic acid (MMF target dose: 3 g/day for 6 months) (Grade A) or low-dose IV-CY (3 g over 3 months) (Grade B) in combination with glucocorticoids, are recommended as initial treatment.

- Corticosteroids: IV-MP 500-750mg ×3 days → oral prednisone 0.5mg/kg ×4 weeks , taper to ≤10 mg/day by 4-6 months (Grade C).

- Based on better efficacy-toxicity (amenorrhea) ratio.

Points to consider:

- Similar recommendation by the ACR: also recommends either MPA or IV-CY: in a following statement they recommend low-dose IV-CY for Caucasians.

- MPA may have greater efficacy in patients of African/Hispanic descent (EULAR & ACR).

- MPA dosage: target MMF dose 3 g/day (EULAR), 2-3 g/day (ACR, lower doses in Asians, higher in severe LN).

- MMF likely to have equivalent efficacy with MPA sodium salt (eMPA) (EULAR & ACR).

- Monitoring MPA blood levels could be helpful to optimize drug exposure (at present not indicated for routine use) (EULAR & ACR).

- Long-term (>5 years) follow-up data are not available for MPA (EULAR & ACR).

- Higher initial GC dose (oral prednisone 0.7-1 mg/kg/day) may be used in severe renal or extra-renal lupus, or when IV-MP treatment is not feasible (EULAR & ACR).

Points to consider. The ACR have made similar recommendations. They did not include the low dose IV cyclophosphamide but they said in a subsequent version that you can use it in Caucasians and in Europeans. MPA may have greater efficacy in patients with African and Hispanic descent and both the EULAR and ACR guidelines suggest that. We think the dosage of MPA for the initial period should be 3 g/day, EULAR. ACR is a little bit more flexible from 2-3 g. Of course, in Asians you should use a lower dose. If you have severe lupus nephritis, then...
you go for 3 g. MMF is likely to have equivalent efficacy with MPA sodium and this is both the EULAR and ACR guidelines. If you can monitor MPA blood levels that could be helpful to optimize drug exposure but in most sites this may not be available. This is something that I think we need to keep in mind as a community of physicians treating these patients. Long-term data that is more than 5 years is not available for patients treated with MMF. You will never see them. Unfortunately, the ALMS study terminated at 5 months, so I don’t want to scare you but I want you to be cautious with your patients with whom you’re using MMF because we don’t know how good it is after 10, 15 or 20 years in contrast with cyclophosphamide for which we do know the long-term efficacy and toxicity. This is just something to watch out for. Again, if you like to use high doses of steroids, you may use them but only for severe and extra-renal manifestations. But if you use these drugs, do not use more than 0.5 g of prednisone. These are young girls; you do not want to make them ---.

Slide 16

Treatment of severe proliferative lupus nephritis

- In patients with adverse prognostic factors (reduced GFR, substantial crescents or fibrinoid necrosis in biopsy), treatment may also include:
  - High-dose IV-CY (monthly pulses 0.75-1 g/m² ×6) (Grade A) or
  - Per os CY (2-2.5 mg/kg ×3 months) (Grade B)

- Mycophenolate is also recommended
  - but, evidence is from non-randomized trials, or post-hoc analyses of RCTs with short-term follow-up (Grade B)

- Crescentic LN: ACR recommends either MMF (3 g/day) or IV-CY in combination with high-dose GC (Grade C)

There is a subset of proliferative patients who have very severe nephritis. These are patients who have the histology features that we see here or decreased GFR and for those people you may use high dose cyclophosphamide, you may use the NIH regimen at least for 6 months or per os cyclophosphamide, grades A and B. This is based on the Lancet paper that was published many years ago. Now what about MMF? Can you use MMF in these patients? We decided yes, you can do that, this information comes from non-randomised trials or post hoc analyses of randomised controlled trials with short-term follow-up. So you may use it but be cautious and this is grade B where for cyclophosphamide for this population of patients is
grade A. ACR claims that you can use MMF in crescentic lupus nephritis, 3 g with grade C, just be careful there’s not enough experience.

Slide 17

What about azathioprine?

Grootscholten et al. KI 2006; Arends et al. ARD 2012

- Azathioprine (2mg/kg/day) may be considered as an alternative to MPA or CY in selected patients without adverse prognostic factors, or when these drugs are contra-indicated, not tolerated or unavailable (Grade B-C).
- Associated with a higher flare risk (Grade B)
- ACR: does not recommend (or considers...) AZA as first-line treatment in LN

What about azathioprine? Is there any role? MMF is not available in poor countries and we have to be practical and deal with this. We feel that at least on the Houssiau side that there is good data suggesting that azathioprine can be a good alternative to MPA or to cyclophosphamide in selected patients without adverse prognostic factors or when these drugs are contraindicated, not tolerated or they are not available. Of course, azathioprine is associated with higher flare risk, so it’s not your first choice but for mild cases you could use azathioprine. ACR does not recommend it as I said.

Slide 18

Class V (membranous) lupus nephritis

- Although considered a more ‘benign’ presentation, ~20-25% will develop chronic renal insufficiency after 10–15 years
- Increased thrombotic complications in patients with nephrotic syndrome

For membranous that’s a point of contention. Nephrologists somehow confuse idiopathic membranous with lupus membranous. I’m not a nephrologist, I’m a rheumatologist and I think there is a difference between lupus and idiopathic. Lupus membranous may have a worse outcome than idiopathic membranous. So, I’m not sure you have to see lupus membranous the same or view it the same way you view idiopathic membranous.

Slide 19

**Treatment of class V (membranous) lupus nephritis**

<table>
<thead>
<tr>
<th></th>
<th>Steroid-only treatment</th>
<th>Non-steroid immunosuppressive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. studies</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>No. patients</td>
<td>136</td>
<td>349</td>
</tr>
<tr>
<td>Gender (♀)</td>
<td>93%</td>
<td>84%</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>63</td>
<td>19</td>
</tr>
<tr>
<td>Mean baseline UPCR</td>
<td>~4.0</td>
<td>~5.0</td>
</tr>
<tr>
<td>Medications</td>
<td>GC only</td>
<td>AZA, MMF/eMPA, CY, CsA, TAC</td>
</tr>
<tr>
<td>Response rate (95% CI)</td>
<td>PR: 20% (4–43%)</td>
<td>PR: 38% (31–45%)</td>
</tr>
<tr>
<td></td>
<td>CR: 39% (27–53%)</td>
<td>CR: 42% (32–53%)</td>
</tr>
<tr>
<td></td>
<td><strong>NR: 39% (21–61%)</strong></td>
<td><strong>NR: 19% (13–26%)</strong></td>
</tr>
</tbody>
</table>


As you know there are trials with MMF in membranous. The question is whether to use immunosuppressive therapy or not? This is a meta-analysis published in the Journal of Investigative Medicine. The bottom line is here, if you use only steroids, the non-responders are 40%. If you do use immunosuppressive drugs in addition to steroids, then the non-responders are lower.

Slide 20
These are the data of Howard Austin. This is our NIH study published in the JASN suggesting that in lupus membranous cytotoxic therapy is superior in IV cyclophosphamide or cyclosporine. Of course, you may argue that we should not have stopped cyclosporine but this is how the study was done.

Slide 21

Treatment of class V (membranous) lupus nephritis: randomized data

- Austin et al. JASN 2009
  - Moderately severe cases (median GFR 80-39 ml/min/1.73m², UPCR 5.0-5.8, SAb 2.5-3.0 g/dL)
  - Superiority of the combination of high-dose IV CY or cyclosporin with GC vs CY alone
  - Predictors for lack of response at 12 months: baseline UPCR >5.0 and treatment with GC alone
  - Ciclosporin: more relapses of nephrotic syndrome than CY

This is the data about the MMF in membranous lupus nephritis. There is not a randomised controlled study; this is sub post hoc analysis of 2 randomised controlled trials. They took all the patients who had membranous and they received MMF and they found that there is comparable efficacy between MMF and IV cyclophosphamide. This is not the best trial but it looks like MMF may be as efficacious. Again, a direct comparison is not available.

Slide 22
So what is our recommendation for this? In pure class V membrane nephritis with nephrotic range of proteinuria, MMF, target dose 3 g/day for 6 months or MPA in combination with oral prednisone (0.5mg/kg/day) may be used based on better efficacy/toxicity ratio. (Grade B)

Alternative options include: CY (Grade A), calcineurin inhibitors (ciclosporin [Grade A; risk for relapses], tacrolimus [Grade B]), or rituximab (Grade C).

Points to consider

- Similar recommendation by the ACR. MPA as first-choice
- Optimal anti-proteinuric treatment (RAAS blockade) is recommended
- The low-dose CY regimen has not been tested in pure class V LN
- Limited data regarding the effects of immunosuppressive treatment on ‘hard’ outcomes
- Treatment of non-nephrotic class V LN? (AZA as steroids-sparing agent, calcineurin inhibitors)

So what is our recommendation for this? In pure class V membrane nephritis with nephrotic range of proteinuria MMF, target dose 3 g/day for 6 months or MPA in combination with oral prednisone may be used based on better efficacy: toxicity ratio. Not because the data is better just because the toxicity is better with MMF. Alternative options include cyclophosphamide (Grade A), calcineurin inhibitors (Grade A), tacrolimus (Grade B) or rituximab (Grade C). The ACR has similar recommendations also, both societies recommend anti-proteinuric therapy. Of note, the low dose cyclophosphamide regimens have not been tested in pure class IV. We do not have any data on hard outcomes. There is no data on the treatment of non-nephrotic class V lupus nephritis and we could not reach a consensus there.

Slide 23

Need for long-term maintenance treatment in lupus nephritis

So this is the induction therapy. What do you do for the maintenance therapy in lupus nephritis? You need maintenance therapy to decrease the relapses.

Slide 24
As you know, there are studies comparing MMF and azathioprine. I will not go over the studies, I will just tell you what our recommendations are. In patients that improve after initial therapy subsequent immunosuppression is recommended with either MPA at lower doses (initial target MMF dose 2g/day) or AZA (2mg/kg/day) for at least 3 years, in combination with low dose prednisone (5-7.5mg/day) (Grade A).

- Gradual drug withdrawal, glucocorticoids first, can then be attempted (Grade C)
- Patients who responded to initial treatment with MPA should remain on MPA unless pregnancy is contemplated, in which case they should switch to AZA (Grade C)
- Calcineurin inhibitors can be considered (Grade C)

Points to consider
- Similar recommendation by the ACR, either MPA or MMF
- Continuing treatment for longer (>3 years) time periods should be individualized

As you know, there are studies comparing MMF and azathioprine. I will not go over the studies, I will just tell you what our recommendations are. In patients that improve after initial therapy subsequent immunosuppression is recommended with either MPA or Azathioprine for at least 3 years in combination with low dose prednisone Grade A. Gradual drug withdrawal, you first withdraw the steroids and then you withdraw the other things. You can use as maintenance either MMF or azathioprine but if you start with MMF and the patient does well, you continue with MMF as maintenance because we have seen cases of relapses of lupus nephritis after switching to azathioprine. So if you start with MMF, it’s probably better to continue with MMF at lower doses and you can use calcineurin inhibitors for prevention of relapses.
Now, what is the target when you treat for lupus nephritis? This is not a trivial question and I will tell you why. This is how we define the complete renal response. If we have proteinuria less than 0.5 g with normal or near normal GFR and partial response, when the proteinuria decreases to 50% to subnephrotic level with normal or near normal GFR, this is the definition that the Milan group put out and has served the community very well. Now, these are the important details. The partial renal response should be achieved preferably within the first 6 months and no later than 12 months after treatment initiation. Although partial renal response carries worse prognosis than complete renal response, it may be an acceptable outcome when all treatments have been exhausted or cannot be used due to high risks for toxicity.

ACR does not have a consensus and this brings us to the refractory lupus nephritis that is about 20 or 30% of lupus patients.
Let me just tell you. So what are our recommendations for the work definition for refractory lupus nephritis? Our recommendation is that refractory lupus nephritis is when there is lack of nay improvement, i.e. no reduction in proteinuria or deterioration in GFR by 3-4 months or if we have not achieved at least partial response by 6-12 months or you have not reached a complete response by 12 months but again, this is expert opinion and these outcomes have not been validated.

Slide 29

**Treatment options in refractory LN**

- **Widely available, no special skills required**
  - Combination of IV-CY and IV-MP
  - MPA
  - IVIG
  - Calcineurin inhibitors (monotherapy or in combination)
  - Rituximab

- **Not widely available, special skills required, use preferably in referral centres**
  - Stem cell transplantation
  - Plasma exchange – immunoadsorption
  - IV-CY mega-therapy
What do you do for refractory lupus nephritis?

**Slide 30**

**B-cell depletion in LN**

- **LUNAR trial**
  - N=144 patients (1:1 placebo:rituximab)
  - Multi-racial
  - Class III-IV (+ V)
  - 56% nephrotic, 26% with GFR <60 ml/min

- Failed to meet its primary end-point

- Significantly better serological improvement (anti-dsDNA, C3) in rituximab-treated patients


**Slide 31**

**B-cell depletion in LN: better outlook in uncontrolled studies**

- N = 300 LN patients (83% Caucasians)
- Active disease under GC plus 1–3 ISTs
- Previous IST used: CY 60%, MPA 47%, AZA 47%

- Efficacy: CR ~40%, PR ~34% (after mean 60 weeks)
- Lower response rates in class V and mixed V+III-IV

**Points to consider**

- May require maintenance immunosuppression (with MMF, AZA, IV-CY)
- Most cases of CR occur during the 2nd year after treatment
- Fares are common (26–30%) but are usually successfully retreated
- ?when to repeat treatment
- ?possible publication bias – reports of modest or non-sustained effect

Weidenbusch. NDT. 2013

You may use rituximab and the randomised controlled trials did not show a benefit but there are good data suggesting that it’s efficacious.

**Slide 32**
There are data suggesting

Slide 33

'Multi-target' immunosuppressive treatment in LN

- RCT in mixed class V-III-IV LN (N=40 Asian patients)
- 65% had received previous treatment with MPA or IV-CY
- Mean UPCR 4.0-4.4; preserved renal function
- Better efficacy of the combination treatment (MMF 2 g/d + TAC 4 mg/d + GC) versus pulses IV-CY (1 g/m²) + GC

Points to consider

- Further randomized data are needed, especially in other ethnic groups
- Increased risk for infections (possibly related to concomitant MPA dose)
- Need to monitor trough blood levels of CNI

that it maybe efficacious.

Slide 34
Let me just tell you what our recommendations are for refractory lupus nephritis. For patients who fail treatment with MPA or CY either because of lack of effect or due to adverse events, we recommend that the treatment is switched:

- from MPA to CY, or (Grade C)
- from CY to MPA, or (Grade C)
- rituximab be given (Grade C) (EULAR + ACR)

Additional options: calcineurin inhibitors, IVIG, plasma exchange for rapidly progressive glomerulonephritis, immunoabsorption.

Let me just tell you what our recommendations are for refractory lupus nephritis. For patients who fail treatment with MPA or cyclophosphamide either because of lack of efficacy or due to adverse events, we recommend a treatment switch. If you're taking MPA or cyclophosphamide, you are using cyclophosphamide or MPA or in both cases you may use rituximab Grade C. Additional options, you can read them here calcineurin inhibitors,

Slide 35

**Do not overlook the comorbidities!**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAAS blockers</strong></td>
<td>UPCR &gt;0.5 or hypertension</td>
<td>Grade B</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>Dyslipidemia (target LDL-C 100 mg/dL)</td>
<td>Grade C</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td>Reduced risk for relapse, damage accrual, cardiovascular events</td>
<td>Grade B</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>Thromboprophylaxis in aPL-positive patients</td>
<td>Grade C</td>
</tr>
<tr>
<td><strong>Calcium and vitamin D</strong></td>
<td>Osteoprotection</td>
<td>Grade C</td>
</tr>
<tr>
<td><strong>Immunizations</strong></td>
<td>Reduction in risk for infections</td>
<td>Grade C</td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
<td>Nephrotic syndrome with severe hypo-albuminaemia (especially if aPL-positive)</td>
<td>Grade C</td>
</tr>
</tbody>
</table>

(EULAR + ACR)

 plasma exchange for

Slide 36
Monitoring lupus nephritis

✓ Active lupus nephritis should be regularly monitored by determining at each visit:
  - body weight
  - blood pressure
  - serum creatinine and eGFR
  - serum albumin
  - Proteinuria (spot UPCR preferred)
  - urinary sediment (microscopic evaluation)
  - serum C3 and C4, anti-dsDNA
  - complete blood cell count (Grade B/C)

✓ aPL antibodies and lipid profile: at baseline and monitored intermittently (Grade B)

✓ Visits: every 2-4 weeks for the first 2-4 months after diagnosis or flare, then according to the response (Grade C)

✓ Monitoring for both renal and extra-renal disease activity: life-long at least every 3-6 months (Grade C)

(EULAR = ACR; the ACR provides time schedule for monitoring)

rapidly progressive glomerulonephritis.

Slide 37

How useful are serological tests in monitoring LN?

<table>
<thead>
<tr>
<th>Test</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum C1</td>
<td>1.6–2.9</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Serum C4</td>
<td>1.1–2.1</td>
<td>0.4–0.9</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>1.5–4.6</td>
<td>0.3–0.8</td>
</tr>
<tr>
<td>Anti-C1q</td>
<td>2.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Points to consider:

✓ The individual predictive value of clinical and laboratory tests for hard outcomes at particular time points is modest

✓ Changes in serological tests are more important predictors of concurrent or impending flare than their absolute levels;

✓ Pre-emptive treatment in the face of deteriorating serology alone is not indicated

I would like
When to repeat kidney biopsy?

- May be considered in selected cases, such as:
  - **worsening or refractoriness to immunosuppressive or biologic treatment** (failure to decrease proteinuria by ≥50%, persistent proteinuria beyond one year, and/or worsening of GFR), or
  - at relapse.

To demonstrate change or progression in histological class, change in biopsy chronicity and activity indices, to provide prognostic information, and detect other pathologies (Grade B)

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**EULAR-ERA 2012 LN recommendations in a nutshell**

- **Acceptable Goals- changes in therapy:**
  - **short term (3-4 months):** improvement any reduction in proteinuria
  - **medium term (6-12 months):** partial response (50% reduction in proteinuria to subnephrotic levels). In long standing disease this is a good as someone could go
  - **long term (1-2 years):** complete response: less than 0.5 gm protein

- **MMF and low-dose IV-CY first choices** based on ease of administration/gonadal toxicity. Severe LN IV-CY/MMF followed by MMF
- **Refractory patients:** switch to the other drug or directly to rituximab
  - Why? Expert opinion
- **Maintenance:** MMF or AZA. If starting with MMF continue with MMF unless pregnancy is contemplated
- **Risk stratification:** for severe LN may use IV-MP with IV-CY or MMF
- **Pediatric lupus:** No significant differences

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This is the summary slide. These are the EULA-ERA lupus nephritis recommendations in a nutshell. Acceptable goals or changes in therapy. In the short-term you should see in the first 3 or 4 months the improvement and a reduction in proteinuria that you're happy with. In the medium-term that is in the first 6-12 months, you should have at least a partial response which is a 50% reduction in proteinuria to subnephrotic levels. In long standing disease this is as good as somebody could go but in the long-term your goal, which is at 1-2 years, should be less than 0.5 g of protein if you can make it and you have to intensify therapy and switch as we said. MMF and low dose IV cyclophosphamide are the first choices based on ease of administration but also on the lack of gonadal toxicity. For severe lupus nephritis you may use the old NIH regimen followed by mycophenolate, the best data is this. The NIH protocol for 6 months followed by MMF. Refractory patients switched to the other drug or directly to rituximab, this is expert opinion. For maintenance you use MMF or azathioprine whatever you
have but if you start with MMF, continue with MMF unless pregnancy is contemplated. As you know, most of lupus patients are in reproductive age and that’s an important consideration. Risk stratification for severe lupus nephritis uses a combination of methylprednisolone with IV cyclophosphamide or MMF and for paediatric lupus we decided there was no significant...