Maintenance of remission, Treatment of Resistant and Relapsing Nephritis

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Major Sections

Maintenance of Remission

Resistant lupus nephritis

Relapse after initial response

Conclusions

MAINTENANCE OF REMISSION

In Whom to Switch to Maintenance?

- Those in remission
- Partial response with predictors of continued remission:
  - Decrease in S. Creatinine
  - Decrease in UTP to <1 g/24 hr

Maintenance Protocols

- Data are limited
- MMF 1-2 g/day or AZA 2 mg/kg/day for at least 3 years, in combination with low-dose prednisone (5–7.5 mg/day)
- Gradual drug withdrawal, GC first, GSA can then be attempted

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Resistant LN

Resistant LN

1. Evidence of unequivocal worsening at the end of 3 mo after the initiation of therapy
2. Failure to achieve partial response after 6–12 months of treatment
3. Failure to achieve complete response after 2 years of treatment

Resistant LN

Resistance to initial treatment

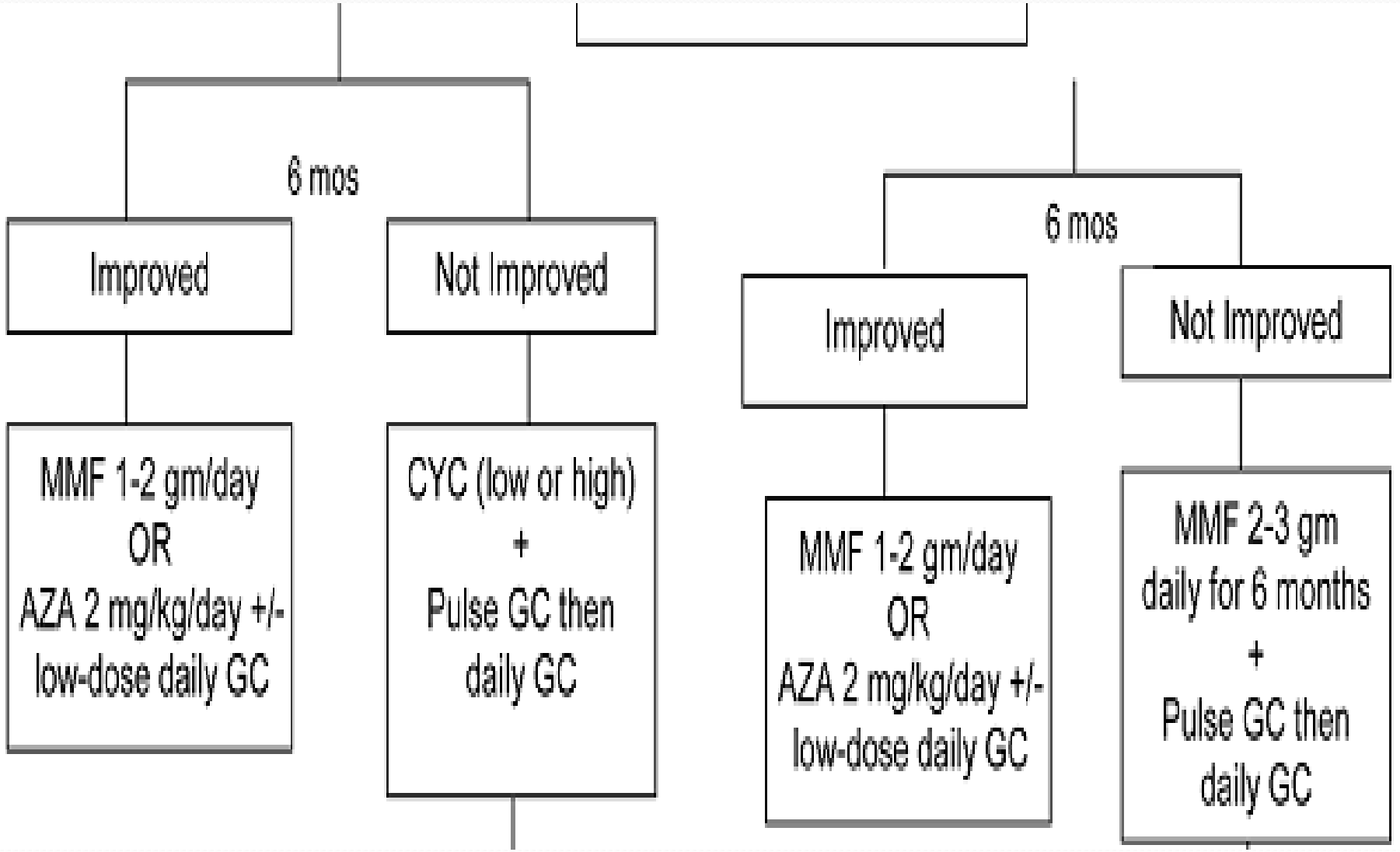
Sequential failure to CYC and MMF

Resistant to Initial Treatment

Options For Initial Resistance

- **CYC resistance:** MMF
- **MMF resistance:**
  - CYC (presumptive ground)
  - MMF + Tacrolimus 0.075 mg/kg/d

ACR 2012 Guidelines: Options For Initial Resistance



Sequential Failure

of

CYC & MMF

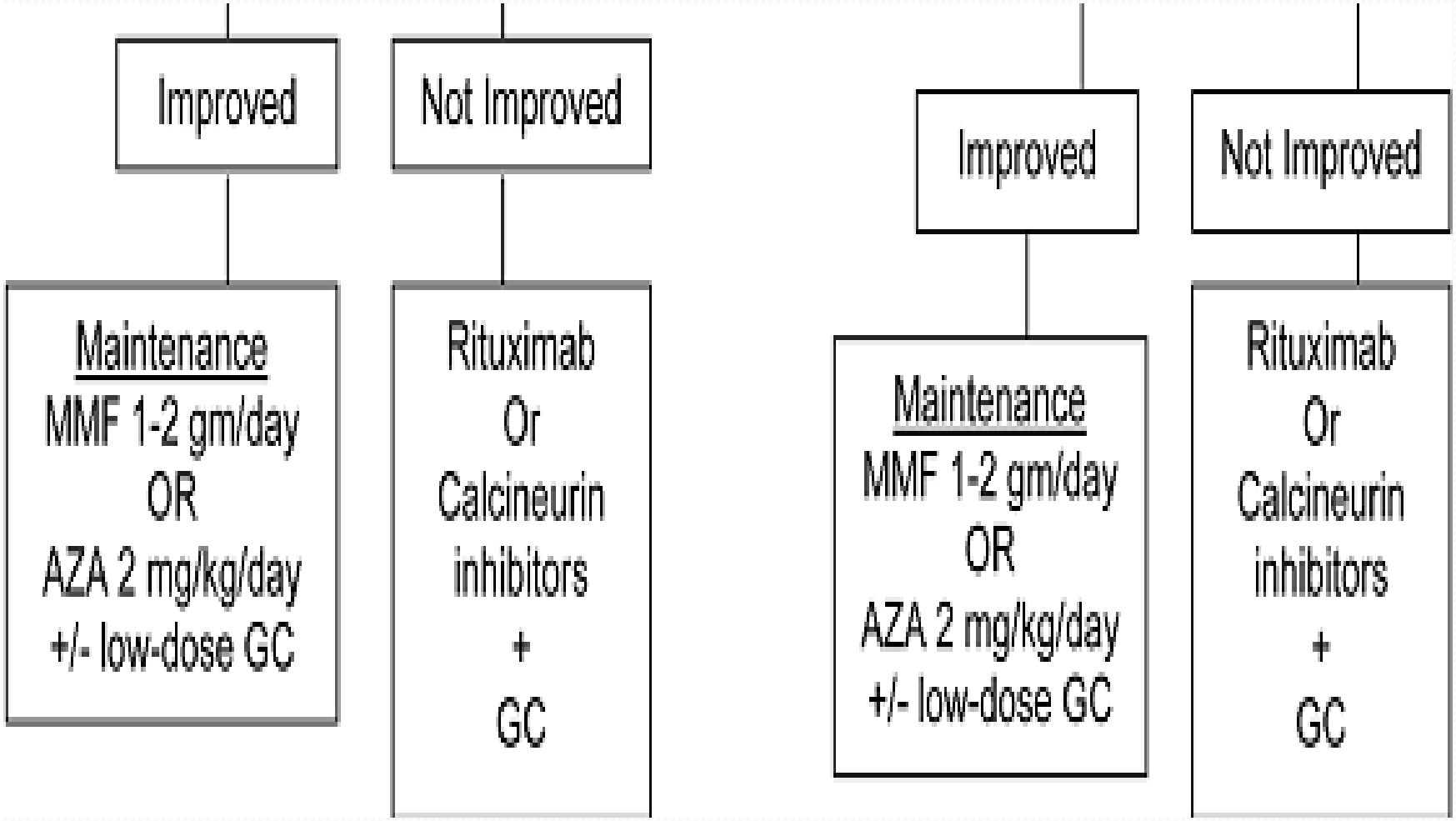
Sequential Failure of CYC & MMF

- Rituximab:
  - Resistance or intolerance to both
  - Intolerance to 1, resistance to the other
  - Severe worsening
- Calcineurin inhibitors (cyclosporine/tacrolimus)
- MMF *plus* tacrolimus
- Belimumab not yet recommended

Scope of Leflunomide in Refractory LN

- Has been used in LN refractory or intolerant to standard immunosuppressive therapy
- Requires a loading dose of 100 mg/day for 3 days followed by 20 mg/day thereafter
- Efficacy safety data limited

ACR 2012 Guidelines: Sequential Failure of CYC & MMF



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AXY

Relapse After Initial Remission

Relapse of LN: Classification

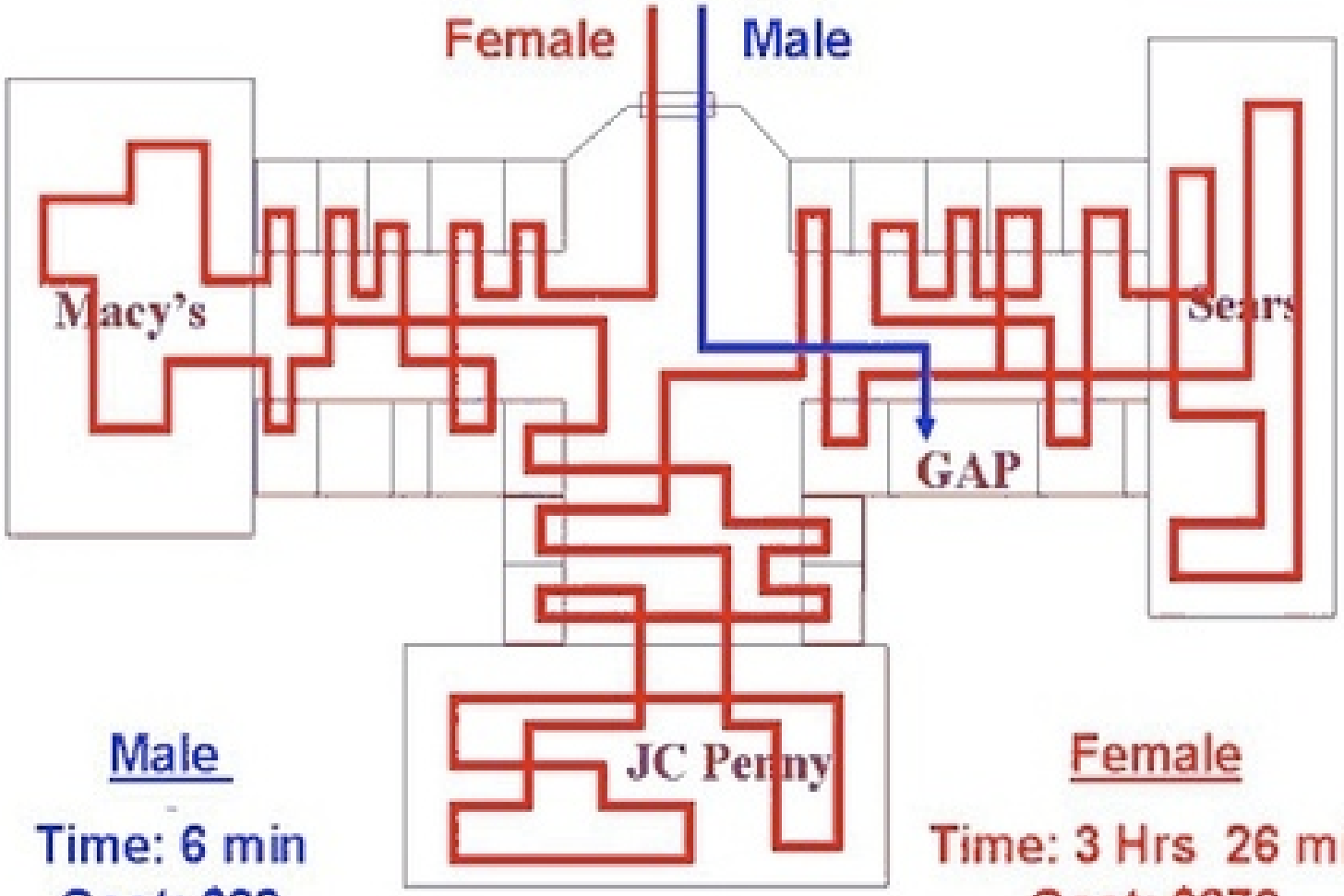
- Nephritic relapse
  - Mild relapse
  - Moderate to severe flare
- Proteinuric relapse
  - On the background of class III or IV
  - On the background of class V

Nephritic Relapses

Nephritic Relapses

- Active urine sediments with ↑ in glomerular hematuria by ≥10 RBCs/hpf, irrespective of changes in urinary protein excretion
  - Mild relapse: increased hematuria with normal S. Cr and GFR
  - Severe relapse: Reproducible ↑ in serum creatinine by ≥30% or ↓ in GFR by ≥10% with or without increase in hematuria

Mission: Go to Gap, Buy a Pair of Pants



Male

Time: 6 min
Cost: $33

Female

Time: 3 Hrs 26 min
Cost: $876

Scheme of Treatment

- Mild nephritic relapse:
  - Initial induction with CYC:
    - AZA maintenance
    - MMF maintenance
    - Off maintenance
  - Initial induction with MMF:
    - AZA maintenance
    - MMF maintenance
    - Off maintenance
- Moderate to severe nephritic relapse:
  - Initial induction with CYC
  - Initial induction with MMF
  - Recurrent moderate-to-severe nephritic relapse

Treatment of Mild Nephritic Relapses: GC

- **On maintenance:**

✓ Prednisolone @ 15 mg/day for a 2-wk period, followed by gradual return to the pre-relapse dose

- **Off maintenance:**

✓ Prednisone 60 mg/day for 1 wk, tapered to 15 mg/day during the first 3 mo of therapy, and then continued for another 3 mo

✓ Thereafter, prednisone dose can be gradually↓ by 2.5 mg/day every 2-3 wks, assuming that there is no further flare or worsening of the renal disease

Treatment of Mild Nephritic Relapses: GSA Initial Induction with CYC

- AZA maintenance: ↑ AZA, particularly if the AZA dose has been tapered, or, if ineffective, switch to MMF
- MMF maintenance: ↑ MMF, or, if ineffective, switch to AZA
  - Off maintenance, MMF may be started

Treatment of Mild Nephritic Relapses: GSA Initial Induction with MMF

- Off maintenance: MMF may be restarted
- On maintenance with lower doses of MMF: MMF dose can be ↑ to 2-3g/day
- On AZA: ↑ AZA to a maximum of 2 to 3 mg/kg/day, as tolerated, until there is a clinical response

Moderate-Severe Nephritic Relapses: Reinduction

- Initial CYC induction & on AZA or off maintenance:
  - MMF is preferred for initial treatment of relapse
  - CYC may be used if cumulative dose <240 mg/kg or <16 g
- Initial MMF induction:
  - No longer taking maintenance : MMF or CYC, CYC preferred
  - Still taking MMF for maintenance therapy: CYC is preferred
    - If the pt is taking a low dose of MMF for maintenance, the dose of this drug can be ↑ to doses recommended for induction therapy

Recurrent Moderate to Severe Nephritic Relapses

Patients who continue to relapse, like those with resistant LN, may benefit from a trial of rituximab

Proteinuric Relapses

Proteinuric Relapses

- Reproducible doubling of UPCR to >100 mg/mmol after complete response or
- Reproducible doubling of UPCR to >200 mg/mmol after partial response
- May occur on the background of
  - Class III/IV
  - Class V

Proteinuric Relapses: Background Class III/IV

- Often there are class V changes
- Repeat biopsy for distinguishing between:
  - Combined proliferative LN & class V LN
    - To be treated as class V
  - Transformation to class V LN…

Protenuric Relapse with Class V Histology

- Nephrotic proteinuria: $\geq$ 3.5 g/day
- Progressively rising creatinine

Proteinuric Relapses: Background Class V: Initial MMF…

- In patients who initially responded to MMF but subsequently relapsed:
  - Relapse during maintenance therapy (when MMF is being tapered) or after MMF has been discontinued: the original dose of MMF should be resumed
  - If the relapse occurs during the 1st 6 mo of MMF treatment, switching to CYC therapy is recommended

Proteinuric Relapses: Background Class V: Initial CYC or CNI

- Most often, patients initially treated with CYC or a CNI are those who have a contraindication to or who cannot tolerate MMF
- Those who do not respond to or who relapse despite CYC treatment should be converted to a CNI
- Those who do not respond to or who relapse despite CNI therapy should be converted to CYC
- However, if a patient who was successfully treated with a CNI, relapsed after the drug has been discontinued, the same can be used a 2nd time

Conclusions

- Resistance and relapses are common
- Keys to success:
  - Structured assessment of response and its proper interpretation
  - Timely switching of strategy
  - Meticulous follow up for early identification of relapses

Thank you!