Expert Panel Guide on Conversion to a Sirolimus-Based Immunosuppressive Regimen and Management of Adverse Events

Wyeth Philippines, Inc

2236 Don Chino Roces Ave., Makati City
Tel Nos. 843-0941 to 50, 844-5902 to 11, 810-0146 to 48
Fax Nos. 817-3523, 810-0146, 813-2162

Transplantation Advisory Board

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Rose Marie R. Liquete, MD
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Indications for Conversion
- Calcineurin Inhibitor (CNI) toxicity
- Chronic Allograft Nephropathy (CAN), biopsy-proven
- Chronic Allograft Dysfunction (CAD), clinical diagnosis\(^1,2\)
- Prevention of CNI toxicity
- CNI Minimization
- CNI Elimination

Types of Conversion
- Conversion after the diagnosis of allograft dysfunction as indicated above
- Occurs from months to years post-transplant
- Abnormal renal function
- Stable conversion
  - Performed at a certain time point post transplant (at least 3 months after transplant)
  - Normal graft function

GUIDELINE 1

Recommended target trough in conversion protocols\(^3-11\)

<table>
<thead>
<tr>
<th>Time Post Transplant</th>
<th>Trough Level (HPLC)</th>
<th>Trough Level (IMX)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year post transplant</td>
<td>8 - 12 ng/mL</td>
<td>9.6 - 14.5 ng/mL</td>
</tr>
<tr>
<td>&gt;1 year post transplant</td>
<td>6 - 12 ng/mL</td>
<td>7.1 - 14.5 ng/mL</td>
</tr>
</tbody>
</table>

* Sirolimus target trough levels in a regimen containing sirolimus + MMF + S
* From IMX® Sirolimus Assay Package Insert, Abbott Diagnostics Division, Abbott Park, IL.

REMARKS: The corollary to immunosuppression in transplantation is that the nearer to the time of transplant, the higher the dose of immunosuppression required to prevent immunologic rejection. The farther away from the time of transplant, the lower the risk for immunologic rejection, and the higher the risk of development of CNI toxicity, and allograft damage from hypertension, diabetes or hyperlipidemia among others.

GUIDELINE 2

Factors associated with successful conversion*:\(^10-14\)
- GFR >40 mL/min
- Serum creatinine <2.5 mg/dl
- Proteinuria <800 mg/day

* Successful conversion implies an improvement or stabilization in renal function following the conversion to sirolimus with either CNI minimization or elimination.

Remarks: Studies have shown that patients who do not fulfill the above are less likely to respond to conversion.

GUIDELINE 3

Regimen for conversion

<table>
<thead>
<tr>
<th>Day</th>
<th>Calcineurin Inhibitor</th>
<th>Sirolimus</th>
<th>MMF/MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reduce by 50%</td>
<td>6 mg OD</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>2</td>
<td>Maintain dose</td>
<td>4 mg OD</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>3</td>
<td>Maintain dose</td>
<td>2 mg OD</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>4</td>
<td>Maintain dose</td>
<td>2 mg OD</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>5</td>
<td>Maintain dose</td>
<td>2 mg OD</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>6</td>
<td>May discontinue if desired Sirolimus trough level is achieved</td>
<td>Check trough and adjust dose accordingly</td>
<td>If Sirolimus level is within desired trough, reduce MMF/MPA by 500/360 mg daily. Daily dose should not be lower than 1 gram/720 mg.</td>
</tr>
</tbody>
</table>

GUIDELINE 4

Mycophenolate Mofetil (MMF)/Mycophenolic Acid (MPA) dose when used in combination with sirolimus

- Once the sirolimus level is 8-12 ng/mL by HPLC, reduce the current dose of MMF/MPA by 500/360 mg daily. However, the daily MMF/MPA dose should not be lower than 1 gram/720 mg per day.

Remarks: The dose of MMF/MPA is higher when used in combination with ciclosporin due to the reduction in enterohepatic recycling of MMF/MPA by ciclosporin\(^15\). This does not occur, however, with either tacrolimus or sirolimus. Thus, the dose of MMF/MPA is lower when used in combination with sirolimus or tacrolimus compared to its dose in combination with ciclosporin.

When ciclosporin is withdrawn from a CNI-MMF/MPA regimen and replaced with sirolimus, a reduction in the MMF/MPA dose is necessary. This is because significantly higher mycophenolic acid (MPA) area under the curve (AUC) and trough concentrations were reported in patients receiving a sirolimus based regimen compared to those receiving a ciclosporin-based regimen.\(^16-22\)
GUIDELINE 5
Management of key adverse events
- should be guided by the target trough levels or the recommended doses of the immunosuppression used.

<table>
<thead>
<tr>
<th>TIME POST TRANSPLANT</th>
<th>SIROLIMUS TROUGH LEVELS (HPLC) NG/ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>&lt;8</td>
</tr>
<tr>
<td></td>
<td>Repeat level within 5-7 days and monitor, if persists reduce MMF/MPA followed by a reduction in SIROLIMUS</td>
</tr>
<tr>
<td></td>
<td>Hold MMF/MPA dose, if persists hold or discontinue SIROLIMUS</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PLATELET COUNT*</td>
<td>&lt;75,000/mm³</td>
</tr>
<tr>
<td></td>
<td>Repeat level within 5-7 days and monitor, if persists reduce MMF/MPA followed by a reduction in SIROLIMUS</td>
</tr>
<tr>
<td></td>
<td>Hold MMF/MPA dose, if persists hold or discontinue SIROLIMUS</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC COUNT*</td>
<td>&lt;3,000/min²</td>
</tr>
<tr>
<td></td>
<td>Repeat level within 5-7 days and monitor, if persists reduce MMF/MPA followed by a reduction in SIROLIMUS</td>
</tr>
<tr>
<td></td>
<td>Hold MMF/MPA dose, if persists hold or discontinue SIROLIMUS</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIGLYCERIDE</td>
<td>&gt;750 mg/dl (&lt;8.5 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>&gt;1000 mg/dl (&gt;11.3 mmol/L)</td>
</tr>
<tr>
<td>CHOLESTEROL</td>
<td>&gt;500 mg/dl (&gt;12.95 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>&gt;750 mg/dl (&gt;12.94 mmol/L)</td>
</tr>
<tr>
<td>SGPT</td>
<td>&gt;3-5x upper limit of normal</td>
</tr>
<tr>
<td></td>
<td>&gt;5x upper limit of normal</td>
</tr>
<tr>
<td>APHTHOUS ORAL ULCERS**</td>
<td>Repeat level within 5-7 days and monitor, if persists reduce MMF/MPA followed by a reduction in SIROLIMUS</td>
</tr>
</tbody>
</table>

* Treatment for hyperlipidemia (statins or fibrates) should be started once the lipid levels are above normal and should be maximized before considering dose changes of immunosuppressive drugs.

** Statins should not be used concomitantly with fibrates due to the risk of myopathy and rhabdomyolysis.

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Sirolimus-Based Immunosuppressive Regimen

REMARKS

• Conversion studies have been performed among patients with low immunologic risk who had either stable4,6,10-12,14 or deteriorating renal function.4,6,10-12,14 Therfore, conversion at this time is not recommend-ed among patients with the following characteristics due to the lack of clinical data:
  • Patients with high PRA
  • Grade III acute or vascular rejection (Banff 1997) in the last 3 months prior to conversion
  • Acute rejection within the past 3 months
  • Grade III CAN (Banff 1997)

• Conversion should be individualized according to the clinical situation of each patient
  • Time after kidney transplantation
    - The risk for acute rejection is highest in the first weeks and months after transplantation (induction phase) and diminishes thereafter (maintenance phase). Immunosuppression should be at its highest level in the early period and should be reduced for long-term therapy.26
  • Concomitant immunosuppression
    - The doses change depending on the con-comitant immunosuppressive medications administered.
  • Immunologic risk
    - Highly sensitized patients with recurring episodes of moderate to severe acute rejec-tions are poor candidates for conversion to sirolimus.

• Proteinuria after conversion to sirolimus.27
  • Proteinuria has been reported in patients converted from a CNI- to a sirolimus-based immunsuppression regimen, sometimes to nephrotic-range. The risk for development of severe proteinuria post-conversion appears to be higher in patients with significant renal injury pre-conversion or in those with pre-existing moderate proteinuria.15,11
  • Careful monitoring of urinary protein excretion is recommended in the conversion setting (re-view of spot urinary protein or 24hr proteinuria at least every 6 months).
  • The use of ACEIs or ARBs has been found to reduce proteinuria and is recommended to be started prior to sirolimus conversion in patients with existing proteinuria. The use of ARBs and ACEIs has allowed the continued use of sirolimus while controlling proteinuria in several studies.8,11,28,29 If, however, nephrotic syndrome develops, discontinuation of sirolimus should be considered and a renal biopsy performed.

REFERENCES

17. Holt, DW et al. MMF may be given at lower doses when used in association with sirolimus in renal transplant recipients [abstract], Am J Transplant 2001; 1(suppl 1):247. Abstract #444.