Management of Post-transplant hyperlipidemia

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Division of Diabetes, Endocrinology and Metabolism
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Learning objectives

• Recognize abnormalities in cholesterol panels

• Identify the mechanisms associated to post transplant dyslipidemia

• Become familiar with treatment options for hypercholesterolemia, hypertriglyceridemia and mixed hyperlipidemia in transplant patients
UNDERSTANDING A CHOLESTEROL PANEL
Cholesterol values

- Total Cholesterol
  
  \[ \text{LDL-C} + \text{HDL-C} + \frac{\text{VLDL}}{5} \]

- Triglycerides
- HDL-C
- LDL-C*

* Calculated value. If Tg > 400 mg/dl LDL cannot be calculated and needs to be measured

**Classification of cholesterol & triglyceride levels in mg/dl**

<table>
<thead>
<tr>
<th>LDL-C</th>
<th></th>
<th></th>
<th>HDL-C</th>
<th></th>
<th></th>
<th>Triglycerides</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Desirable</td>
<td>Below desirable</td>
<td>&lt;40 (men)</td>
<td>Low</td>
<td></td>
<td>&lt;150</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>100–129</td>
<td>Above desirable</td>
<td>Borderline high</td>
<td>&lt;50 (women)</td>
<td>Low</td>
<td></td>
<td>150–199</td>
<td>Borderline high</td>
<td></td>
</tr>
<tr>
<td>130–159</td>
<td>High</td>
<td>Borderline high</td>
<td></td>
<td></td>
<td></td>
<td>200–499</td>
<td>High</td>
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<tr>
<td>160–189</td>
<td>High</td>
<td>Borderline high</td>
<td></td>
<td></td>
<td></td>
<td>≥500</td>
<td>Very high†</td>
<td></td>
</tr>
<tr>
<td>≥190</td>
<td>Very high</td>
<td>Very high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Most common dyslipidemias

- Hypercholesterolemia
- Mixed hyperlipidemia
- Hypertriglycerideridemia
Lipid Clinic – 3 new patients

Mrs. A  Mr. B  Ms. C
### Mrs. A

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Patient’s results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TC</strong></td>
<td>&lt;200</td>
<td>210</td>
</tr>
<tr>
<td><strong>Tg</strong></td>
<td>&lt;150</td>
<td>88</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>&gt;50</td>
<td>49</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>&lt;130</td>
<td><strong>143</strong></td>
</tr>
</tbody>
</table>

**Hypercholesterolemia**

Cholesterol values are in mg/dl.
<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Patient’s results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;200</td>
<td>329</td>
</tr>
<tr>
<td>Tg</td>
<td>&lt;150</td>
<td>1457</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt;40</td>
<td>36</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;130</td>
<td>128</td>
</tr>
</tbody>
</table>

**Hypertriglyceridermia**

Cholesterol values are in mg/dl.
Ms. C

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Patient’s results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;200</td>
<td>302</td>
</tr>
<tr>
<td>Tg</td>
<td>&lt;150</td>
<td>260</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt;50</td>
<td>74</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;130</td>
<td>176</td>
</tr>
</tbody>
</table>

Mixed Hyperlipidemia

Cholesterol values are in mg/dl.
TRANSPLANT & HYPERLIPIDEMIA
Transplant & Hyperlipidemia

Factors associated with lipid abnormalities

Immunosuppressive drugs

When to check a lipid panel

Cardiovascular disease & transplant

Prevalence
Transplant & Hyperlipidemia

Factors associated with lipid abnormalities

Immunosuppressive drugs

When to check a lipid panel

Cardiovascular disease & transplant

Prevalence
Prevalence of hyperlipidemia in patients s/p organ transplant

HCT= allogenic hematopoietic stem cell transplantation
HLD= hyperlipidemia, LDL=hypercholesterolemia, Tg=hypertriglyceridemia

World J Transplant 2016;6(1):125-134
Ther Adv Endocrinol Metab 2016;7(3) 110-127
Current pharmaceutical design, 2006 (12): 4771-4783
Cardiol Clin 21(2003) 377-392
Bio Blood Marrow Transplant 2015(21):809-820
Transplant & Hyperlipidemia

Prevalence

Factors associated with lipid abnormalities

Immunosuppressive drugs

Cardiovascular disease & transplant

When to check a lipid panel
Cardiovascular disease (CVD) & transplant

• CVD is a *common cause* of morbidity and mortality among long term transplant survivors

• 1\textsuperscript{st} cause of death in heart & kidney transplant recipients

• 2\textsuperscript{nd} cause of death in liver transplant recipients

• CVD causes late mortality:
  – 40% after cardiac and renal transplantation
  – 20% after liver transplantation
  – 5% after lung transplantation

• Atherosclerosis $\rightarrow$ accelerated after transplantation
Hyperlipidemia & transplant

• Incidence ↑ after organ transplantation

• Risk factor for CVD

  *Interventions for hyperlipidemia have an impact on reducing cardiac deaths and non-fatal MI in clinical trials specific to the transplant population*

• Risk factor for long-term graft loss

  *Hyperlipidemia is a possible contributor to chronic kidney allograft injury as a non immune risk factor*
Lipid lowering therapy & transplant

• National Kidney Foundation Kidney Disease Quality Outcomes Initiative guidelines:
  – Transplanted patients are included in the highest risk category (considered in the highest ASCVD risk group) (2004)
  – Consider renal transplant as a coronary heart disease equivalent risk (2004)
  – Statins should be prescribed adults >30 yrs. of age & s/p kidney transplant regardless of their baseline cholesterol level (2013)

• Absence of guidelines for other transplant recipients → consider placing these patients in the high risk category

ASCVD – atherosclerotic cardiovascular disease
ALERT Trial

Assessment of Lescol in Renal Transplantation

- RCT, double blind, placebo controlled

- 2102 renal transplant recipients taking cyclosporine (TC 154-347 mg/dl), age 30-75.

- Fluvastatin 40-80 mg (n=1050) or Placebo (n=1052) for 5 - 6 yrs

- 1ary endpoint – Major Adverse Cardiac Event (cardiac death, nonfatal MI or coronary intervention procedure)

Lancet 2003;361:2024-2031
ALERT Trial - Results

- Mean follow up: 5.1 yrs
- Adverse effects were similar in both groups
- Fluvastatin lowered LDL-C by 32%
- Risk reduction for the 1ary end-point was not significant RR 0.83 (95% CI, 0.64-1.06, p=0.139)

Lancet 2003;361:2024-2031
ALERT Trial – Results cont.

- Post hoc analysis -> fluvastatin therapy was associated
  - 38% reduced risk of cardiac death (p=0.031)
  - 32% risk reduction for definite nonfatal MI (p=0.048)
  - Resulted on a significant risk reduction of the combined end point (cardiac death and non fatal MI) by 35% (p=0.005)
Statins & heart transplant

- RCTs have shown that *pravastatin* & *simvastatin*
  - Improve survival
  - ↓ incidence of acute rejection
  - ↓ transplant vasculopathy

- All patients receive a statin after cardiac transplantation regardless of their baseline LDL-C
Transplant & Hyperlipidemia

Prevalence

Factors associated with lipid abnormalities

Cardiovascular disease & transplant

Immunosuppressive drugs

When to check a lipid panel
Transplant & Hyperlipidemia

Prevalence

Cardiovascular disease & transplant

Factors associated with lipid abnormalities

Immunosuppressive drugs

When to check a lipid panel
Immunosuppression & hyperlipidemia

Calcineurin inhibitors
- Cyclosporine - ↑ LDL
- Tacrolimus – ↑ LDL (possibly)

Antimetabolites
- Azathioprine
- Mycophenolate sodium

mTOR Inhibitor
- Sirolimus – ↑ LDL & Tg
- Everolimus – ↑ LDL

Corticosteroids
- ↑ Tg & LDL
- **Cyclosporine:**
  - Binds to the LDL-R → ↑ LDL-C levels
  - ↑ activity of hepatic lipase → IDL @ LDL
  - ↓ activity of lipoprotein lipase
  - ↓ bile acid synthesis → down regulates LDL-R
  - Highly lipophilic, it is transported in LDL-C particles
  - Effect is dose dependent

- **Tacrolimus:**
  - Produces less lipid disturbance

↑ TC, ↑ Tg, ↑ VLDL & ↑ LDL
Sirolimus:
- Impairs lipoprotein lipase
- ↑ secretion of VLDL
- May cause hepatic over production of lipoprotein
- Dose dependent effect

↑ TC, ↑Tg & ↑LDL
Corticosteroids

- **Increase:**
  - FFA synthetase
  - hepatic synthesis of VLDL
  - VLDL → LDL
  - HMG-CoA reductase activity

- **Decrease:**
  - lipoprotein lipase activity
  - synthesis of LDL-R

↑ ↑ Tg , ↑ TC, ↑ LDL & ↓ HDL

Ther Adv Endocrinol Metab 2016;7(3) 110-127
Current pharmaceutical design, 2006 (12): 4771-4783
Balancing immunosuppression & hyperlipidemia

• Immunosuppressive therapy takes precedence

• Possible changes in immunosuppression:
  – Cyclosporine → tacrolimus
  – Stop sirolimus
  – Low dose steroids
Transplant & Hyperlipidemia

Factors associated with lipid abnormalities

When to check a lipid panel

Cardiovascular disease & transplant

Immunosuppressive drugs
Pre transplant

2/3/6 months post transplant or after a change in treatment

- Dietitian consult
- @ 3 m reassess
- Drug therapy
- @ 3 m reassess

Annually

NKF K/DOQI clinical practice guidelines 2004
World J Transplant 2016; 6(1):125-134
When should a lipid panel be checked? cont.

• **2013 KDIGO guidelines**
  – Initial presentation

  – Suggest
    • No follow up is required for many patients
    • Follow up when results will alter management

  – Reasons to repeat a lipid panel
    • Assessment of adherence
    • Concern about the presence of a new secondary cause for dyslipidemia
When should a lipid panel be checked? cont.

- **American Association for the Study of Liver Disease 2012 Guidelines**
  - Measurement of a fasting lipid panel annually

- **s/p hematopoietic stem cell transplant patients**
  - Annual fasting lipid panel
    - Patients on immunosuppression
    - Have chronic GVHD
    - Previous abnormal lipid profile
TREATMENT OF POST TRANSPLANT HYPERLIPIDEMIA
Treatment overview

Non-pharmacologic

• Dietitian

Pharmacologic

• Started 3 months after lifestyle interventions
Therapeutic lifestyle changes

• **Diet**
  – Saturated fat \(<7\%\) of total calories
  – Polyunsaturated fat up to **10\%** of total calories
  – Monounsaturated fat up to **20\%** of total calories
  – Total fat 25-35\% of total calories
  – Carbohydrates 50-60\% of total calories
  – Fiber 20-30 g per day

• **Physical Activity**
  – 3-4 times per week 20-30 minutes

• **Habits**
  – Smoking cessation
  – Alcohol in moderation
Mrs. A

• 41 y.o.
• s/p double lung transplant – 6 yrs ago
• Migraines

• Medications:
  – Tacrolimus
  – Azathioprine
  – Prednisone
  – Topiramate

• Hyperlipidemia hx:
  – Dx – 1 yr. ago
  – Hypercholesterolemia
  – Atorvastatin - myalgias
  – Rosuvastatin - myalgias
  – No h/o ASCVD
  – Fam Hx premature heart disease
    • P-aunt MI in her 40s
    • P-GF MI in his 40s
    • P-GM MI in her 40s

ASCVD – atherosclerotic cardiovascular disease
Mrs. A

<table>
<thead>
<tr>
<th></th>
<th>Pre Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>186</td>
</tr>
<tr>
<td>Tg</td>
<td>65</td>
</tr>
<tr>
<td>HDL</td>
<td>73</td>
</tr>
<tr>
<td>LDL</td>
<td>100</td>
</tr>
</tbody>
</table>
Mrs. A

<table>
<thead>
<tr>
<th></th>
<th>Pre Tx</th>
<th>2 yrs ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>186</td>
<td>171</td>
</tr>
<tr>
<td>Tg</td>
<td>65</td>
<td>98</td>
</tr>
<tr>
<td>HDL</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>LDL</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>
Mrs. A

<table>
<thead>
<tr>
<th></th>
<th>Pre Tx</th>
<th>2 yrs ago</th>
<th>1 yr. ago*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>186</td>
<td>171</td>
<td>207</td>
</tr>
<tr>
<td>Tg</td>
<td>65</td>
<td>98</td>
<td>78</td>
</tr>
<tr>
<td>HDL</td>
<td>73</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>LDL</td>
<td>100</td>
<td>86</td>
<td>143</td>
</tr>
</tbody>
</table>

*Her dose of tacrolimus was increased 6 m prior to this test from 0.5 mg bid to 2 mg bid.
Mrs. A

<table>
<thead>
<tr>
<th></th>
<th>Pre Tx</th>
<th>2 yrs ago</th>
<th>1 yr. ago*</th>
<th>Current**</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>186</td>
<td>171</td>
<td>207</td>
<td>210</td>
</tr>
<tr>
<td>Tg</td>
<td>65</td>
<td>98</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>HDL</td>
<td>73</td>
<td>65</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>LDL</td>
<td>100</td>
<td>86</td>
<td><strong>143</strong></td>
<td><strong>143</strong></td>
</tr>
</tbody>
</table>

*Her dose of tacrolimus was doubled 6 m prior to this test from 0.5 mg bid to 2 mg bid

**Elevated lipoprotein (a)**
## Treatment of hypercholesterolemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL % reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>18-63</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>18</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>15-30</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>5-25</td>
</tr>
</tbody>
</table>

Lipid academy 9/2015, www.lipid.org
Management of hypercholesterolemia in transplant recipients

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>100-129 mg/dl</th>
<th>&gt;130 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal*</td>
<td>&lt;100 mg/dl</td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td>Initiate</td>
<td>TLC</td>
<td>TLC + low dose statin</td>
</tr>
<tr>
<td>Increase</td>
<td>TLC + low dose statin</td>
<td>TLC + 50% max dose statin</td>
</tr>
<tr>
<td>Alternative</td>
<td>Ezetimibe</td>
<td>Ezetimibe</td>
</tr>
</tbody>
</table>

* If the patient has a history of ASCVD – goal <70 mg/dl
TLC therapeutic lifestyle change

2012 Practice guideline by AASLD and the American Society of Transplantation
<table>
<thead>
<tr>
<th>Risk category</th>
<th>Criteria</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
</table>
| Low           | 0–1 major ASCVD risk factors  
   Consider other risk indicators, if known | <130 LDL-C, mg/dL  
   <100 LDL-C, mg/dL | ≥190 Non-HDL-C, mg/dL  
   ≥160 LDL-C, mg/dL |
| Moderate      | 2 major ASCVD risk factors  
   Consider quantitative risk scoring  
   Consider other risk indicators* | <130 LDL-C, mg/dL  
   <100 LDL-C, mg/dL | ≥160 Non-HDL-C, mg/dL  
   ≥130 LDL-C, mg/dL |
| High          | ≥3 major ASCVD risk factors  
   Diabetes mellitus (type 1 or 2)†  
   0–1 other major ASCVD risk factors and  
   No evidence of end-organ damage  
   Chronic kidney disease stage 3B or 4‡  
   LDL-C of ≥190 mg/dL (severe hypercholesterolemia)§  
   Quantitative risk score reaching the high-risk threshold¶ | <130 LDL-C, mg/dL  
   <100 LDL-C, mg/dL | ≥130 Non-HDL-C, mg/dL  
   ≥100 LDL-C, mg/dL |
| Very high     | ASCVD  
   Diabetes mellitus (type 1 or 2)  
   ≥2 other major ASCVD risk factors or  
   Evidence of end-organ damage¶¶ | <100 LDL-C, mg/dL  
   <70 LDL-C, mg/dL | ≥100 Non-HDL-C, mg/dL  
   ≥70 LDL-C, mg/dL |
Statins
Cholesterol absorption inhibitor
Bile acid sequestrants
Niacin
- Statins
- Cholesterol absorption inhibitor
- Bile acid sequestrants
- Niacin

Block cholesterol synthesis

Upregulate LDL receptors

Modulate inflammatory molecules

Clinically proven to ↓mortality & recurrent cardiovascular events
• Stabilizes & ↓ progression of atherosclerotic plaque

• Antioxidant effect
  – ↓ oxidation of LDL may improve vascular function.
  – Oxidized LDL particles play a key role in atherosclerotic plaque formation

• Inhibits:
  – migration of macrophages
  – smooth muscle cell proliferation
• Side effects:

  – 1-2 % ↑liver enzymes, reversible

  – 5-10% myopathy

  – Rhabdomyolysis

  – Development of diabetes mellitus

  – Memory problems
• Risk of myopathy is greatest ...

  – Elderly
  – GFR < 30 mL/min
  – Maximum statin dose
  – Combination with CYP450 inhibitors
• Patient reports myalgias → check a CK

• 3 to 5 times upper limit of normal → recheck the level weekly

• > 5 times upper limit of normal → d/c
Incidence of fatal rhabdomyolysis

• Per 1 million prescriptions by drugs is:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>0%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.04%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.04%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>0.12%</td>
</tr>
</tbody>
</table>
Statin drug-drug interaction

• Simvastatin and lovastatin
  – Metabolized CYP450- 3A4
  – Contraindicated with cyclosporine

• Rosuvastatin
  – Maximum dose is 5 mg /daily when used with cyclosporine

• Fibrates
  – Gemfibrozil inhibits glucuronidation and uptake of active forms by OATP1B1 transporter by the liver
Table 32. Effects of Cyclosporine on Blood Levels of Statins in Kidney Transplant Recipients.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Increase in the Statin’s AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrovastatin&lt;sup&gt;346&lt;/sup&gt;</td>
<td>8-fold</td>
</tr>
<tr>
<td>Cerivastatin&lt;sup&gt;a347&lt;/sup&gt;</td>
<td>5-fold</td>
</tr>
<tr>
<td>Simavastatin&lt;sup&gt;348&lt;/sup&gt;</td>
<td>3-fold</td>
</tr>
<tr>
<td>Simavastatin&lt;sup&gt;349&lt;/sup&gt;</td>
<td>8-fold</td>
</tr>
<tr>
<td>Lovastatin&lt;sup&gt;350&lt;/sup&gt;</td>
<td>2-fold</td>
</tr>
<tr>
<td>Lovastatin&lt;sup&gt;351&lt;/sup&gt;</td>
<td>3-fold</td>
</tr>
<tr>
<td>Lovastatin&lt;sup&gt;352&lt;/sup&gt;</td>
<td>20-fold</td>
</tr>
<tr>
<td>Pravastatin&lt;sup&gt;352&lt;/sup&gt;</td>
<td>5-fold</td>
</tr>
<tr>
<td>Fluvastatin&lt;sup&gt;353&lt;/sup&gt;</td>
<td>2-fold&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Withdrawn, <sup>b</sup>P>0.05

Abbreviation: AUC, area under the concentration-time curve.
### Recommended statin doses for adults s/p kidney transplant

<table>
<thead>
<tr>
<th>Statin</th>
<th>mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>(40)-80</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>(10)-20</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>(5)-10</td>
</tr>
<tr>
<td>Simvastatin / ezetimibe</td>
<td>20/10</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>(20)-40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>(20)-40</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2</td>
</tr>
</tbody>
</table>

Doses in ( ) are starting doses and recommended doses when patients are in cyclosporine.

Lipid abnormalities after renal transplantation uptodate.com

Table 31. Recommended Daily Statin Dose Ranges.\(^a\)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Level of GFR (mL/min/1.73 m(^2))</th>
<th>With Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥30</td>
<td>&lt;30 or dialysis</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-80 mg</td>
<td>10-80 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-80 mg</td>
<td>10-40 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20-80 mg</td>
<td>10-40 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20-40 mg</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-80 mg</td>
<td>10-40 mg</td>
</tr>
</tbody>
</table>

\(^a\)Adult Treatment Panel III recommendations for GFR ≥30 mL/min/1.73 m\(^2\).\(^{[R3]}\) Most manufacturers recommend once daily dosing, but consider giving 50% of the maximum dose twice daily.
• Binds to cholesterol transporter & blocks its absorption
• May increase LDL-R and also lower plasma LDL-C

Courtesy of MacRae Linton, MD
• Ezetimibe 10 mg daily

• 2nd choice in patients who do not tolerate a statin

• Used in combination with a statin

• Smaller dose (5mg/daily?) due to its interaction with cyclosporine which can induce a 2 to 12 fold ↑ in ezetimibe levels
• Low risk of serious side effects

• Reports:
  – Myalgias
  – Rhabdomyolysis
  – Hepatitis
  – Acute pancreatitis
  – Thrombocytopenia
Hepatic bile acid pool

↑ hepatic bile acid synthesis from cholesterol

↓ intrahepatic cholesterol pool

↓ LDL-C

↑ LDL clearance

↑ LDL receptors

Statins

Cholesterol absorption inhibitor

Bile acid sequestrants

Niacin

Cholesterol absorption inhibitor

Bile acid sequestrants

Niacin
<table>
<thead>
<tr>
<th>Statins</th>
<th>Cholesterol absorption inhibitor</th>
<th>Bile acid sequestrants</th>
<th>Niacin</th>
</tr>
</thead>
</table>

- Gastrointestinal side effects – most common
- Interfere with the absorption of the immunosuppressive drugs
- Can raise triglycerides
- Should be separately administered from them:
  - 1 hour before
  - 4 hours after
↓ release of fatty acids from adipose tissue

↓ FFA  $\rightarrow$  ↓ Tg synthesis

↓ VLDL secretion

↓ LDL-C
• Side effects:
  – Flushing
  – Hepatotoxicity
  – Hyperglycemia
  – Hyperuricemia
  – Gastrointestinal discomfort (nausea, vomiting, dyspepsia)
Mrs. A

• Three months on a low fat diet

• At three months
  – Statin
  – Ezetimibe
Mr. B

- 44 y.o. male
- h/o ESRD s/p kidney transplant – 6 m ago
- Type 2 diabetes
- Hypertension

**Medications:**
- Tacrolimus 3 mg bid*
- Mycophenolate mofetil
- Pravastatin 40 mg daily

**Hyperlipidemia Hx:**
- Dx 2 yrs. prior to tx
- Hypertriglyceridemia
- Prior med: fish oil
- No h/o pancreatitis

* His dose was decreased from Tacrolimus 5 mg bid 3 months ago
Mr. B cont.

<table>
<thead>
<tr>
<th></th>
<th>Pre Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
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<td>LDL</td>
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<td>HbA1c</td>
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### Mr. B cont.

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<tr>
<td>HbA1c</td>
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<tr>
<td>GFR</td>
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<td>&gt;60</td>
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</table>
Hypertriglyceridemia

• Indication for pharmacologic treatment:
  – Tg > 500 mg/dl

• Goal $\rightarrow$ prevent pancreatitis (Tg > 1000 mg/dl)
Hypertriglyceridemia cont.

- Treat secondary etiology

- Diseases:
  - Diabetes
  - Nephrotic syndrome

- Lifestyle:
  - Diet high in simple carbohydrates
  - Alcohol
Hypertriglyceridemia cont.

• Drugs:
  – Immunosuppressant agents
  – Estrogen
  – Glucocorticoids
  – Beta blockers
  – Retinoids
Hypertriglyceridemia management

• Tg < 500 mg/dl
  – Lifestyle modification

• Tg > 500 mg/dl
  – Fibrates
    • Fenofibrate
    • Gemfibrozil
  – Omega 3 fatty acids (DHA & EPA)
    • 4 grams daily (2 grs bid)
## Treatment of hypertriglycerideridemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tg % reduction</th>
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<tbody>
<tr>
<td>Fibrates</td>
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<tr>
<td>Omega-3 fatty acids</td>
<td>45</td>
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<tr>
<td>Statins</td>
<td>7-30</td>
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<tr>
<td>Nicotinic acid</td>
<td>20-50</td>
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</table>

Lipid academy 9/2015, www.lipid.org
• Activate PPAR α

• ↓ hepatic VLDL cholesterol synthesis

• ↑ lipoprotein lipase activity

• Doses need to be adjusted according to the patient’s kidney function
Fibrates

• Adverse effects:
  – GI – dyspepsia, diarrhea
  – Increase LFTs
  – May potentiate action of anticoagulation

• Contraindications
  – Hepatic impairment
  – Pre-existing gallbladder disease
• May reversibly ↑ creatinine

• Myotoxicity
  – fenofibrate is preferred over gemfibrozil when added to a statin
In transplant ...

- Evidence supporting the safety and efficacy of fibrate use is weak

- Dose adjusted for kidney function

- Not recommended

- Only on Tg >1000 mg/dl
• Unclear mechanism of action

• EPA – eicosapentaenoic acid
• DHA – docosahexaenoic acid

• Omega-3: four grams daily (divided doses)
Mr. B

- Dietitian
- Omega 3 fatty acids—2 grs bid
- Diabetes control
Ms. C

- 52 y.o.
- s/p bilateral lung transplant – 3 m ago
- Hypertension
- Hypothyroidism

Medications:
- Tacrolimus 3.5 mg bid
- Azathioprine
- Prednisone 15 mg
- Levothyroxine

Hyperlipidemia Hx:
- Dx 15-20 yrs prior to transplant
- Hypercholesterolemia
- Pre transplant:
  - Atorvastatin
  - Rosuvastatin (stopped at the time of tx)
- No h/o ASCVD
- No Fam Hx premature heart disease
<table>
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<tr>
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<th>Pre Tx</th>
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</thead>
<tbody>
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<td>TC</td>
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<tr>
<td>Tg</td>
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<tr>
<td>HDL</td>
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<tr>
<td>LDL</td>
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Ms. C

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Pravastatin 10 mg daily
Ms. C – 3 months later

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<tr>
<td>GFR</td>
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Pravastatin 20 mg daily
Ms. C – 6 months later

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Pravastatin 40 mg daily
Ms. C – 9 months later

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Pravastatin 40 mg daily
When should you refer a patient to a lipid specialist?

- If the patient’s LDL > 190 mg/dl or triglycerides >1000 mg/dl

- The patient has a prior history of intolerance to cholesterol lowering medications

- If combination therapy is not controlling your patient’s cholesterol level
THANKS

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