Update on PCSK9 inhibitors and Statin Intolerance

Dr Amrish Agrawal
MD, DM Card, MRCP UK, FRCP(Glas.), FRCP(Edin.)
Fellow Cardiology (Australia), FCSI
Consultant Cardiologist
Ass. Professor of Medicine
Fujairah Hospital, UAE
Definition of Statin Intolerance (SI):
A Clinical Syndrome (ie there is no specific test yet) that

Characterized by inability to use statins for long-term lipid and/or CV risk reduction

Practically, at least 2 statins

Not due to:
Predisposing factors or interactions

Due to:
• Significant or alarming symptoms (most commonly muscle pain and/or fatigue)
  AND/OR
• Biomarker abnormalities attributed temporally and unequivocally to statin use
• As generally determined by re-challenge

Mancini GB et al, Can J Cardiol 2013;29:61553-1568

Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016)
### Consensus group

<table>
<thead>
<tr>
<th>EAS Consensus Panel</th>
<th>Definition</th>
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### Trial

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| ODYSSEY ALTERNATIVE  
Alirocumab | **Intolerance to 2 statins**, including one at the lowest approved starting dose  
(Included a placebo run-in and statin rechallenge arm) |
| GAUSS-2  
Evolocumab | **Intolerance to 2 statins**, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects |
| GAUSS-3  
Evolocumab | **Intolerance to 3 statins or 2 statins** (one of which was atorvastatin 10 mg/day) or with a history of marked CK elevation accompanied by muscle symptoms while on a statin |
**Definition of Statin Associated Muscle Symptoms:**

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**2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapy**

...unacceptable muscle-related symptoms that resolve with **discontinuation** of therapy and occur with **rechallenge**:

- on at least 2 to 3 statins, preferably
- ones that use different metabolic pathways
- and have different lipophilicity,
- and 1 of which is prescribed at the lowest approved dose.

- **Alirocumab**
  - Intolerance to 2 statins, including one at the lowest approved starting dose (Included a placebo run-in and statin rechallenge arm)

- **Gauss-2**
  - **Evolocumab**
    - Intolerance to 2 statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects

- **Gauss-3**
  - **Evolocumab**
    - Intolerance to 3 statins or 2 statins (one of which was atorvastatin 10 mg/day) or with a history of marked CK elevation accompanied by muscle symptoms while on a statin
### Patterns of Statin Muscle Intolerance (EAS Consensus Panel):

<table>
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<th>Description</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Muscle Symptoms + Normal CK</td>
<td>Myalgia, may be related to Statin SAMS</td>
</tr>
<tr>
<td>Muscle Symptoms + CK ≤ 10x ULN</td>
<td>Statin Associated Muscle Symptoms (SAMS)</td>
</tr>
<tr>
<td>Muscle Symptoms + CK ≥ 10X ULN</td>
<td>Myositis/myopathy</td>
</tr>
<tr>
<td>Myonecrosis + CK elevation ≥ 40x</td>
<td>+/-Myoglobinuria, Rhabdomyolysis</td>
</tr>
</tbody>
</table>

Effects potentially involved in statin related muscle symptoms
Effects potentially involved in statin related muscle symptoms

Needham et al. Statin Myotoxicity. Neuromuscl Disord 2014;24:4-15
Therapeutic flow-chart for management of patients with SAMS by the EAS Consensus Panel:

If CK < 4X₅ ULN:
- Washout: 2-4 weeks
- If symptoms improve: Second statin at usual or starting dose
- Symptom Reoccur: low dose of 3rd potent statin, consider one/twice weekly

If CK ≥ 4X₅ ULN:
- Washout: 6 weeks if
- If symptoms improve: low dose 2nd statin, dose consider one/twice weekly

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

What “Options” we have for Statin Intolerance?

- Ezetimibe
  - NPC1L1 Inhibitors
- Bile Acid Sequesterants
- PCSK9 Inhibitors
- LDL Reduction
  - mAbs
ESC Lipids 2016 and EAS Consensus Document:

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

Ezetimibe

LDL reduction by 15-20%
ESC Lipids 2016 and EAS Consensus Document:

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

Ezetimibe

- LDL reduction by 15-20 %
- Also 15-20 %
  - A] + bile acid absorption inhibitor
  - B] + fibrate (not gemfibrozil)
  - A + B
ESC Lipids 2016 and EAS Consensus Document:

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

Ezetimibe

LDL reduction by 15-20 %

Also 15-20 %

A] + bile acid absorption inhibitor
B] + fibrate (not gemfibrozil)
A + B

If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

PCSK 9 inhibitors
PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting Them for Lysosomal Degradation

### FDA Approved Indications for Anti-PCSK9 Monoclonal Antibodies (Diet + Max. Tolerated Statin Therapy for Additional LDL-C Lowering)

<table>
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<tr>
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<th>Clinical ASCVD*</th>
<th>Heterozygous FH</th>
<th>Homozygous FH</th>
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<tbody>
<tr>
<td>Evolocumab</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>+</td>
<td>+</td>
<td>-</td>
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*Clinical ASCVD includes acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.
Should PCSK9 Inhibitors be Used in Statin Intolerant Patients?

It depends on whom you ask

• “Patients” and “Providers”
• Pharmaceutical Companies
• Payers and Insurance
• Professional Organizations (NLA, ACC, AHA, ECS and EAS)
Evolocumab

- GUASS 1 (2012): effect of Evolocumab versus placebo in statin-intolerant patients
- GUASS 2 (2014): Evolocumab in Patients With Statin Intolerance
- GUASS 3 (JAMA 2016): Evolocumab Superior to Ezetimibe in Patients With Muscle-Related Statin Intolerance

Alirocumab

- ODYSSEY ALTERNATIVE
Cohort of 300 patients SI to at least 2 statins randomized to Ezetimibe vs SC evolocumab

- LDL C decrease by around 55%
- absolute 38% more than ezetimibe
- 70-90% of the patients were at the LDL target goal
Efficacy and Tolerability of **Evolocumab vs. Ezetimibe** in Patients with Muscle-Related Statin Intolerance

**The GAUSS-3 Randomized Clinical Trial**

Nissen SE, et al [published online ahead of print April 3, 2016]

Steven E. Nissen, MD\(^1\); Erik Stroes, MD, PhD\(^2\); Ricardo E. Dent-Acosta, MD\(^3\); Robert S. Rosenson, MD\(^4\); Sam J. Lehman, MBBS, PhD\(^5\); Naveed Sattar, MD, PhD\(^6\); David Preiss, MD\(^7,8\); Eric Bruckert, MD\(^9\); Richard Češka, MD\(^10,11\); Norman Lepor, MD\(^12\); Christie M. Ballantyne, MD\(^13\); Ioanna Gouni-Berthold, MD\(^14\); Mary Elliott, MS\(^3\); Danielle M. Brennan, MS\(^1\); Scott M. Wasserman, MD\(^3\); Ransi Somaratne, MD, MBA\(^3\); Rob Scott, MD\(^3\); Evan A. Stein, MD, PhD\(^15\)

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GAUSS-3 = **Goal** **Achievement after** **Utilizing an anti-PCSK9 antibody in** **Statin Intolerant** **Subjects-3**
Efficacy and Tolerability of **Evolocumab vs. Ezetimibe** in Patients with Muscle-Related Statin Intolerance

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**Patients with history of statin intolerance defined as:**
- inability to tolerate atorvastatin 10 mg QD and any other statin at any dose OR
- inability to tolerate ≥ 3 statins\(^1\) OR
- documented history of CK elevation >10 x ULN with muscle symptoms while on statins
The GAUSS-3 Randomized Clinical Trial

PART A

Period 1

Period 2

Washout and screening

LDL-C not at NCEP ATP III goal

1:1

Patients with documented CK > 10 x ULN on statin with muscle symptoms

4–8 weeks

Atorvastatin

20 mg

Placebo

Atorvastatin

20 mg

Placebo

Patients Enter Part B Directly

PART B

W10

W12

W16

W20

W22

LDL-C not at NCEP ATP III goal

1:1

Patients with documented CK > 10 x ULN on statin with muscle symptoms

4–8 weeks

Day 1

W24

W48

Washout

and screening

W10

W12

W16

W20

W22

W
The GAUSS-3 Randomized Clinical Trial

**PART A**
- Period 1
- Period 2
- Evolocumab SC + Placebo PO
- Placebo SC + Ezetimibe PO
- Atorvastatin 20 mg
- Placebo

**PART B**
- 218 Qualified for Phase B
- Evolocumab SC
- Placebo SC + Ezetimibe PO
- Placebo PO

**PART C**
- 2-Year OLE

**Washout and screening**
- LDL-C not at NCEP ATPIII goal
- 1:1

**Patients with documented CK > 10 x ULN on statin with muscle symptoms**
- 26.5% of patients had myalgias associated with placebo but not with statin
- only 43% had a true intolerance to statins.

**Patients Enter Part B Directly**

4-8 weeks

Day 1 W10 W12 W16 W20 W22 W24 W48

Confidence 2017
GAUSS-3: Phase B: Percent Change in LDL-C Level & lipid parameters

Percent Change From Baseline in LDL-C

-37.8%
P < 0.001

Ezetimibe N = 73
Evolocumab N = 145

GAUSS-3: Phase B: Percent Change in LDL-C Level & lipid parameters

<table>
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<tr>
<th>Study Week</th>
<th>Ezetimibe N = 73</th>
<th>Evolocumab N = 145</th>
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<tr>
<td>Baseline</td>
<td>72</td>
<td>142</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>142</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>139</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>137</td>
</tr>
<tr>
<td>16</td>
<td>64</td>
<td>127</td>
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<tr>
<td>20</td>
<td>60</td>
<td>127</td>
</tr>
<tr>
<td>22</td>
<td>57</td>
<td>117</td>
</tr>
<tr>
<td>24</td>
<td>-60</td>
<td>-50</td>
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Percent Change From Baseline in LDL-C

-37.8%

Study Week

Mean Difference in Cosecondary Efficacy Endpoints

Ezetimibe (n = 73) Evolocumab (n = 145)

-11% -14% -11% -12% -12%

-38% -47% -45% -41% -46%

Mean TC non-HDL-C ApoB TC/HDL-C ratio Apo B:A1

Ezetimibe Evolocumab

P < 0.001

GAUSS-3:
Phase B: Time to First Occurrence of a Muscle-related AE

Cumulative Event Probability

Days Following Randomization

HR: 0.68
95% CI: 0.39–1.19
P = 0.17

28.8% Ezetimibe
1 out of 145

20.7% Evolocumab
5 out of 73

Ezetimibe
Evolutomab
GAUSS 3 Conclusions:

• ...... the use of evolocumab compared with ezetimibe resulted in a **significantly greater reduction in LDL-C** and other atherogenic lipoproteins after 24 weeks.

• Both ezetimibe and evolocumab were **well tolerated** during the trial, with 5 out of 73 ezetimibe patients (6.8%) and 1 out of 145 evolocumab patient (0.7%) discontinuing active treatment due to muscle-related adverse events.

• However, 11 evolocumab-treated patients (7.6%) discontinued oral placebo for muscle symptoms.
ODYSSEY ALTERNATIVE: Efficacy and safety of alirocumab versus ezetimibe, in patients with statin intolerance defined by placebo run-in and statin rechallenge arm

Patrick M. Moriarty¹, Paul D. Thompson², Christopher P. Cannon³, John R. Guyton⁴, Jean Bergeron⁵, Franklin J. Zieve⁶, Eric Bruckert⁷, Terry A. Jacobson⁸, Marie T. Baccara-Dinet⁹, Jian Zhao¹⁰, Yunling Du¹⁰, Robert Pordy¹¹, Daniel Gipe¹¹

¹Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA; ²Hartford Hospital, Hartford, CT, USA; ³Harvard Clinical Research Institute, Boston, MA, USA; ⁴Duke University Medical Center, Durham, NC, USA; ⁵Clinique des Maladies Lipidiques de Québec Inc., Québec, Canada; ⁶McGuire VA Medical Center, Richmond, VA, USA; ⁷Hospitalier Pitié-Salpêtrière, Paris, France; ⁸Emory University, Atlanta, GA, USA; ⁹Sanofi, Montpellier, France; ¹⁰Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; ¹¹Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

ClinicalTrials.gov identifier: NCT01709513
Journal of Clinical Lipidology 2015:9, 758-769
DOI: 10.1016/j.jacl.2015.08.006
ODYSSEY ALTERNATIVE Study Design

Double-Blind Treatment Period (24 Weeks)

Alirocumab 75/150 mg SC Q2W + placebo PO QD
administered via single 1 mL injection using prefilled pen for self-administration

Per-protocol dose ↑ possible depending on W8 LDL-C

Ezetimibe 10 mg PO QD + placebo SC Q2W

N=100

Atorvastatin 20 mg PO QD + placebo SC Q2W

N=50

Placebo Oral OD

+ Placebo SC Q2W†

N=100

OLTP/8 week FU

Assessments

W -4 W0 W4 W8 W12 W16 W24

Patients discontinued if muscle-related AEs reported with placebos during run-in

Per-protocol dose increase if Week 8 LDL-C ≥70 or ≥100 mg/dL (depending on CV risk)

Primary endpoint
(LDL-C % change from baseline, ALI and EZE only)
Safety analysis (all groups)

4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.
OLTP: Alirocumab open-label treatment period; W, Week.

Statin intolerant patients*
(by medical history)
with LDL-C ≥70 mg/dL (very-high CV risk) or ≥100 mg/dL (moderate/high risk)

*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in
Alirocumab Maintained LDL-C Reductions Week 4–24

**Time-on-treatment analysis**
(modified ITT – observed data only)

**LDL-C, mean (SE), mg/dL**

- **Alirocumab**
- **Ezetimibe**

**Week 12:**
- 150 mg Q2W

**Week 24:**
- Δ 59 mg/dL
- 157 mg/dL

**Week 24:**
- Δ 65 mg/dL
- 92 mg/dL

49.5% received 150 mg Q2W at W12

**Legend:**
- Alirocumab
- Ezetimibe
Alirocumab Maintained LDL-C Reductions Week 4–24

Significantly More SI Patients Achieved Target LDL-C <70 or <100 mg/dL (depending on CV risk) with Alirocumab vs Ezetimibe

- **Alirocumab** vs **Ezetimibe**

**On-treatment**

- All patients received 150 mg Q2W at W12

**Week 24**

- **Alirocumab**: 49.5% received 150 mg Q2W at W12
- **Ezetimibe**: 6% received 150 mg Q2W at W12

**% pts reaching LDL-C goal at W24**

- **ITT**: 42% vs 4%
- **On-treatment**: 51% vs 6%

*P < 0.0001*
Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event†

Cox model analysis:
HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P=0.042
HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P=0.096

†Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
ALI, alirocumab; ATV, atorvastatin, EZE, ezetimibe.
So PCSK9i work in Statin Intolerance, But do we have outcome data?

No outcome trials with PCSK9 inhibitors in population with statin Intolerance
Summary of FOURIER

• ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
• ↓ CV outcomes in patients already on statin therapy
• Evolocumab was safe and well-tolerated

![Graph showing LDL-C levels and CV outcomes over time](image)

- **Placebo**
  - 59% mean decline
  - P<0.00001
  - Absolute ↓ 1.45 mM (1.42-1.47)

- **Evolocumab**
  - Median 0.78 mM
  - IQR [0.49-1.27]

- **CV death, MI, stroke, UA, cor revasc**
  - HR 0.85 (0.79-0.92)
  - P<0.0001

- **CV death, MI, stroke**
  - HR 0.80 (0.73-0.88)
  - P<0.00001

Guidelines on the Use of PCSK9i in Statin Intolerance

- **2016**
  - ESC Dyslipidemia Guidelines 2016
- **April 2017**
  - AACE lipid guidelines, April 2017
- **May 2017**
  - NLA
- **Aug 2017**
  - 2017 ESC/EAS consensus Statement for use of PCSK9i (Section on SI )
- **Oct 2017**
  - 2017 ACC Expert Consensus on the Role of Non-Statin Therapies (Section on SI )
ESC/EAS Task Force Consensus on PSCK9i: Population with SAMS:

Not at LDL-C Goal--- With ASCVD < 70(1.8) or without ASCVD < 100 (2.6)

- Consider PCSK9 inhibitor treatment to attain LDL-C goal (<1.8 mmol/L or <70 mg/dL in patients with ASCVD; <2.6 mmol/L or <100 mg/dL in patients without ASCVD)

- Ezetimibe 10 mg ± bile acid sequestrant should be considered

- ASCVD or diabetes with target organ damage or a major risk factor⁵ and LDL-C >3.6 mmol/L or >140 mg/dL. Refer to Figure 1

- Rapid progression of ASCVD and LDL-C >2.8 mmol/L or >100 mg/dL**. Refer to Figure 1

- FH without ASCVD, with or without additional risk factors and elevated LDL-C. Refer to Figure 2
Conclusions:

• Despite our best efforts, there will be a population who will have Statin Intolerance (full or partial) which will not allow to reach LDL-C goals.

• Use non-statins such as Ezetimibe and BAS may help as adjuncts if needed to achieve lipid targets.

• PCSK9 inhibitors are reasonable options in high risk patients and shown to reduce LDL by 50-60% in SI patients.

• The data from the long term outcomes and safety studies in this subset will better inform the true value of PCSK9i therapy.
References:

- Erik S. Stroes et al. European Heart Journal. 2015:36, 1012–1022
- Journal of Clinical Lipidology 2015:9, 758-769, DOI: 10.1016/j.jacl.2015.08.006