Statin-induced Myotoxicity: Initial Case Characteristics and Efficiency of Recruitment

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Abstract

In general, statins are well-tolerated. Statin-induced myotoxicity can be accompanied by a variety of pain syndromes.

Subjects were recruited through a large multi-specialty group practice located in Central Wisconsin. From a medical record representing ~2 million unique subjects, we identified 13,901 potential study participants through an electronic query targeting statin exposure and clinical lab data. Subject records with creatine kinase (CK) values in the upper 10th percentile (CK > 438 U/l) were further characterized through manual data abstraction. Eligibility was determined based upon physician notes reflecting index of suspicion. Subjects were excluded if the CK level had been drawn during evaluation for an acute coronary syndrome or trauma. Subjects were also excluded if they had chronic kidney disease (creatinine level > 2.0), liver disease (AST or ALT > 200), or pre-existing muscle disease.

From the first 1085 subject records, 172 met inclusion criteria (15.9% eligibility). Of the first 146 subjects invited to participate, 113 agreed to provide informed consent and a blood sample for extraction of DNA. They represent 59 atorvastatin cases, 29 pravastatin cases, and 23 simvastatin cases. The first 50 atorvastatin cases were reviewed by a licensed practicing physician. Two cases were removed (equivocal exclusion criteria), and the remaining 48 cases were graded using binary variables to describe the clinical pain syndrome: 28/48 (58.3%) had diffuse pain (versus focal), 24/48 (50%) had proximal pain (versus distal), and 18/48 (37.5%) had severe pain (versus mild).

While electronic text mining is an efficient way to screen large numbers of medical records for potential cases of statin-induced muscle damage, manual chart abstraction is still required. A large subset of validated atorvastatin cases had either proximal pain, diffuse pain, or severe pain (70.3%).

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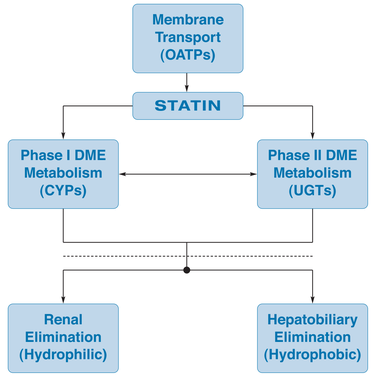
Background I

- Statins represent one of the most commonly prescribed class of drugs in the world.
- Statins are considered both safe and efficacious.
- Statin-induced muscle complications vary along a clinical continuum
  - myalgia
  - myopathy
  - rhabdomyolysis
- Rhabdomyolysis is extremely rare in subjects receiving statin monotherapy [Graham DJ 2004].
- Genetic variability in statin metabolism may influence subject risk [Wilke 2005].

Figure 1: Statin Disposition



Goals of Current Study

- Describe process of case finding for statin induced myotoxicity.
- Quantify process efficiency for enrollment of PARC myotoxicity cases.
- Report characteristics for the first 50 cases of atorvastatin induced myotoxicity.

Recruitment Process

- Electronic text mining was initially used to screen potential subjects.
- Potential study subjects were screened for eligibility by a trained research co-coordinator.
- The first 50 atorvastatin cases were reviewed by a licensed practicing physician (RKM).

Criteria

Inclusion

- Atorvastatin or Simvastatin or Pravastatin
- CK upper 10th percentile (> 438 units/L) during time of statin intolerance
- High Physician index of suspicion (ADR suspected)

Exclusion

- CK drawn for suspected acute coronary syndrome
- CK elevation secondary to trauma
- Pre-existing kidney disease, defined as creatinine > 2.0
- Pre-existing liver disease, defined as AST or ALT > 200 prior to event.
- Pre-existing neuromuscular disorder or inflammatory muscle disease

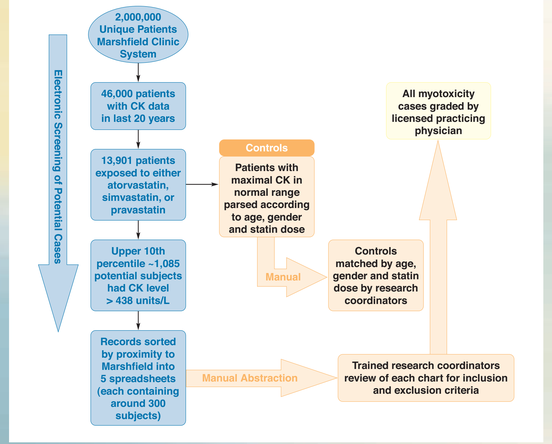
Pharmacogenomics and Risk of Cardiovascular Disease (PARC)

- Program Project Grant
  - Multicenter
  - Retrospective
- Endpoints
  - Efficacy
  - Toxicity
- Atorvastatin
  - Myalgias
  - High CK
- Phenotyping
  - Research coordinator
  - Physician review
- Genotyping
  - Candidate gene
  - Genome scan
- Analysis
  - Univariate
  - Multivariate
- Validation
  - Simvastatin
  - Pravastatin
- Reproducibility
  - United States
  - United Kingdom

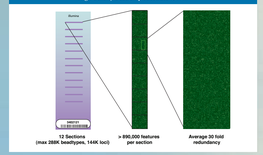
Candidate Gene Approach

CYP 2C9		CYP 2D6 (Cont.)		CYP 3A4	
*1	Wild type	*4A	C 188 T	*1A	Wild type
*2	C 430 T		C 0162 A A 1072 G C 1085 G G 1749 C G 1934 A G 4268 C	*1B	A-290G
*3	A 1075 C			*2	T 754 C C 1062 A
CYP 2D6				**CYP 3A5**	
*1A	Wild type	*4B-L	C 188 T + others	*1A	Wild type
*2A	C-1496 G A-1147 G C-652 T G-590 A G 1749 C C 2938 T G 4268 C	*5	Gene deletion	*3A	A 6986 G C 31611 T
		*6A	71795 del	*3B	C 3705 T 3709/10 Insert G A 6986 G C 31611 T
		*6B-D	T-1795 del + others		
		*9	AGA 2701 – 2703 del	*3C	A 6986 G
*2B	C 1127 T G 1729 C C 2938 T G 4268 C	*10A	C 188 T G 1749 C G 4268 C	**UGT 1A1**	
				*1	Wild type
*2XN	N = 2,3,4,5 or 13 G 1749 C C 2938 T G 4268 C	*10B	C 188 T C 1127 T G 1749 C G 4268 C	*6	G 211 A
				*28	Variable n: (TA, Ntaa in promoter TATA box
*3A	A 2637 del			**OATP-C**	
*3B	A 1837 G A 2637 del			*1A	Wild type
				*1B	A 388 G
				*5 T	T 174 C
				*15	A 388 G T 174 C

Figure 2: Case Screening



Genome Scanning Approach



Case Grading – Pain Syndrome

Distribution	Location	Severity	Frequency	Percent
Focal	Proximal	High	5	10.4
Focal	Proximal	Low	1	2.1
Focal	Distal	Low	2	4.2
Diffuse	Proximal	High	10	20.8
Diffuse	Proximal	Low	4	8.3
Diffuse	Distal	High	1	2.1
Diffuse	Distal	Low	9	18.8
Diffuse	Cannot determine	High	2	4.2
Diffuse	Cannot determine	Low	2	4.2
Cannot determine	Cannot determine	Cannot determine	12	25.0

Case Grading – Covariates

Contributory Factor	Yes		No	
	Number	Percent	Number	Percent
Vigorous physical exercise	10	20.8%	38	79.2%
Comorbid hypothyroidism	6	12.5%	42	87.5%
Concomitant gemfibrozil	2	4.2%	46	95.8%
Concomitant fenofibrate	2	4.2%	46	95.8%
Concomitant niacin	4	8.3%	44	91.7%

Results – Efficiency

- 1,085 potential cases were reviewed manually for eligibility.
- 172 patients out of 1085 potential cases (15.9%) were found to be eligible.
- 146 patients out of 172 eligible (84.9%) were sent letters for recruitment.
- 113 patients out of 146 receiving letters (77.4%) chose to enroll.
  - 59 atorvastatin cases
  - 29 pravastatin cases
  - 23 simvastatin cases

Results – Grading

- 2 cases were removed during review by a licensed practicing physician due to equivocal exclusion criteria.
- 48 cases were further graded using binary variables to describe the clinical pain syndrome.
- 28 patients (58.3%) had diffuse pain.
- In 12 patients (25%) the pain syndrome could not be characterized using any of the three parameters (severity, location, localization).
- 6 patients had concomitant hypothyroidism.
- 10 patients reported recent vigorous exercise.

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