Patient-Targeted Adverse Event Surveillance (AES): Use For Hypothesis Generation

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Background

WE HYPOTHESIZED THAT PATIENT-TARGETED AE SURVEILLANCE WOULD:

A. YIELD ADDITIONAL REPORTS

B. ALLOW COLLECTION OF NEW KINDS OF DATA

C. SPEED IDENTIFICATION OF POSSIBLE NEW EFFECTS

D. FACILITATE HYPOTHESIS GENERATION

Status of Effort

- 750 SURVEYS COMPLETED TO DATE (PRIOR TO WEB LAUNCH)
- WEB-BASED SURVEY GENERATED
- WEB-BASED SURVEY LAUNCH EXPECTED IN JANUARY
- HYPOTHESES A, B, AND C SUPPORTED

Results

a. Additional reports? YES

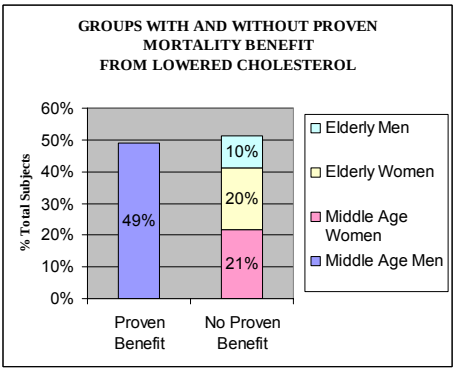
Example:

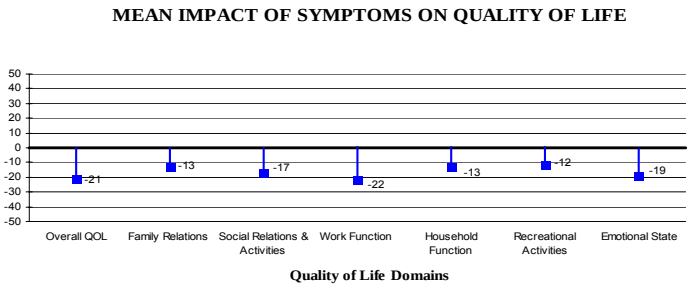
- 55% of physicians reportedly denied possibility of a drug connection when neuropathy arose on statins
- No possible connection per MD → no MD ADR report.

*Literature suggests 16/17 likelihood statins are to blame if no other known neuropathy risk factor. Neurology 58: 1333-1337

b. New information on known ADRs: YES

Example: Cognitive questionnaires, N = 73, mean age 62 (range 34-86)





- DOSE EFFECT (BY ON/OFF/ON)
- QOL IMPACT
- ONSET TIME SHORTER ON RECHALLENGE
- CONCURRENT ADRS

c. Identify possible new ADRs? YES

Examples:

- GLUCOSE ELEVATION (Since then, supported by PROVE-IT/TIMI)
- NEUROPATHY (Since then, supported by case control, Neurology 58: 1333-1337)
- TRANSIENT GLOBAL AMNESIA
- NEURODEGENERATION (Causality less clear for neurodegeneration)

d. Assist hypothesis generation? SEE NEXT PANEL

Representative Cases

Picture has been covered to protect subject privacy (Consent was given by subjects and family for use of photo and name for the original venue.)

Cognitive

Mrs. [redacted] Encinitas, CA:

"I guess you have to experience it to know what it means to have lost your mind – and get it back with something so simple [as stopping the statin]. It's totally changed my life."

(Mrs. [redacted] had presumed early Alzheimer's and was felt unable to care for herself. Her family was looking into assisted-living. Her family stopped her atorvastatin and cognitive function reportedly normalized completely in three days. Later, four subsequent statin trials and one ezetimibe trial all resulted in serious cognitive deterioration, normalizing with discontinuation – more slowly with the final agent. She is now off statins and active in the community.)

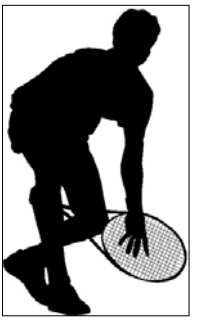
Muscle

Mr. [redacted] Chicago, IL

"It was almost like dying. The muscle problems progressed, till pain was unbearable and my legs gave out and I couldn't walk or even stand. I was hospitalized and had 64 major tests for every disease including MS. Tests included a CT, myelogram, MRI, three EMGs and a muscle biopsy. When I stopped the Lipitor* the improvement was immediate, and I could walk within days. Full recovery has been gradual. Five years later I am at 90-95% of where I was, and every year some things seem to get closer to where I started."

*Only after a family member communicated with Dr. Golomb.

(Mr [redacted] was able to quickly return to work as VP of an insurance company. He is again an avid tennis player.)



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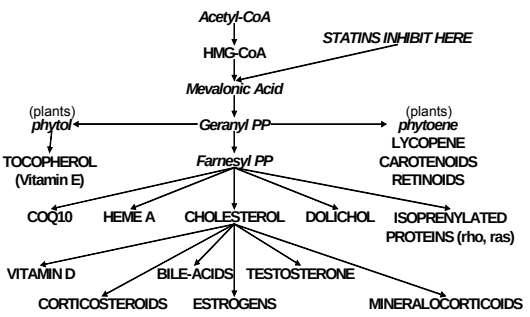
Degenerative Disease (Conjectural relationship to statins)

Mr. [redacted] W. Virginia:

"With the first statin I got pain in my shoulders. I stopped it. I was put on a different statin and got pain in my buttocks; I stopped it. I was put on one or two more statins, and got pain again and stopped. After one month on the next drug, in addition to pain and weakness I got twitching in one arm. By the time I saw my cardiologist, both arms and my chest twitched. He looked at me, said to put my clothes back on and that he didn't need to see me again. That son of a bitch knew he killed me and sent me home."

(Mr. [redacted] was diagnosed with ALS. He lost use of hands, bulbar function, and finally legs. He died of ALS complications in March 2005 – though he never fully met criteria for this condition. He was persuaded till the end that the statins played a role in his illness.)

Background for Hypothesis Generation



STATIN BENEFITS	STATIN HARMS
ANTIOXIDANT (↑ENOS)	PROOXIDANT (↓COQ_{10})
↓INFLAMMATION	↑INFLAMMATION
↓ATHEROSCLEROSIS	↓O_2 UTILIZATION
↑ENDOTHELIAL FXN	↓ATP PRODUCTION
↑PERFUSION	↓MITOCHONDRIAL FXN
↑O^2 DELIVERY	↓CELL BARRIER FXN
↓THROMBOSIS	↓FSV DELIVERY

SOME MEVALONATE PRODUCT FUNCTIONS (AMONG MANY)

- CELL ENERGY, MITOCHONDRIAL FUNCTION – COQ10; HEME-A
- ANTIOXIDATION: COQ10, FSVs
- MITOCHONDRIAL PROTECTION – COQ10, FSVS
- PROTECTION VS. AGING AND APOPTOSIS/NEURODEGENERATION – Q10, FSVS
- PRENYLATION – NEEDED FOR MB ASSOCN & BIOL ACTIVITY OF RAS & OTHER SIGNAL TRANSDUCTION PROTEINS

Background for Hypothesis Generation

SOME CHOLESTEROL FUNCTIONS

- TRANSPORTS FAT SOLUBLE VITAMINS (**FSVs**)
- PRECURSOR TO VITAMIN D & STEROID HORMONES
- TRANSPORTS DETOXIFYING ENZYMES
- REGULATES MEMBRANE (**MB**) FUNCTION, TRANSMEMBRANE EXCHANGE, MB ASSOCIATED ENZYMES
- PRESERVES MEMBRANE POTENTIAL FOR CELLS AND ORGANELLES – CELL ENERGY PRESERVATION
- CONSTITUENT OF MYELIN: CHOLESTEROL = WHITE MATTER SIGNAL ON MRI
- NEEDED FOR SYNAPSE FORMATION
- REGULATES NEUROTRANSMITTER FXN – REUPTAKE, RECEPTOR EXPRESSION

Hypothesis Generation Status

Study	Motivation – AE surveillance	Backup Rationale – Literature	Agency/Status
Statins & Q_{10}: Effects on skeletal & cardiac (ECHO) muscle & mitochondrial (**Mt**) fxn *RO1: RCT*	Subjects cite skeletal & (occasionally) cardio-myopathy	• Statins ↓Q_{10}, Heme-A, Mt fxn • Muscle AEs linked to ↓ Mt fxn • Q_{10} helps ↑ Mt fxn	NHLBI – Not funded
Q_{10}: Does it improve statin muscle AEs*? RO1: RCT*	Some subjects cite Q_{10} benefit Q_{10} to muscle AEs	Same as above	NHLBI – Not funded
Q_{10}: Does it protect against "aging" *R34: R01 Planning Grant*	Many subjects frame complex of statin AEs in terms of aging (e.g." I'm 40 and feel 85")	• Statins ↓ Mt fxn • ↓ Mt fxn = major theorized underpinning of "aging"	NIA – Funded 8-05
Statins & Neurodegeneration: Is there a connection? *RO1: Finland databases*	Neurodegen onset with statins – many reports. Causal or incidental?	• Statins ↓ Q_{10} • Q_{10} admin prevents & retards neurodegeneration – in animals & people	NINDS – Pending
Q_{10}: Does it retard. progression of CV risk factors? *RO1: RCT*	Worsening of glycemia in some, resolves with statin D/C (Supported by PROVE-IT/TIMI)	• Statins ↓ Q_{10} • Q_{10} ↓ glucose; HTN; CRP; lipids (& prevents atorva tachyphylaxis): prelim evidence	NHLBI/NIDDK – Pending
Do statins impair – & Q_{10} improve – energy & Mt fxn by 31P-MRS & biopsy; do they do so selectively in those with muscle AEs *RO1: Randomized Crossover*	Statin AE sufferers cite muscle and energy problems; and improvement with Q_{10} in some	• Statins change bioenergetics • Statins assoc with Mt dysfxn in those with AEs – small study • Q_{10} improves Mt fxn in those with Mt dysfxn • Q_{10} reported to ↓ statin AEs	NIH – Pending

Conclusions

Patient-targeted Adverse Event Surveillance can:

- Secure additional reports
- Gather richer information
- Suggest putative new AEs – for further testing
- Facilitate hypothesis generation – for testing

Acknowledgments

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