Early Development
Biostatistics

Making better use of early phase safety data

Laurence Colin / Yue Li

May 10, 2019

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Safety is a major cause of failed drug approvals

Table 5. Frequency of Safety, Efficacy, CMC, and Labeling Deficiencies for Drugs Failing First-Cycle Review

Type of Deficiency	First-Cycle Review Failures (n = 151)	Delayed Approvals Following Resubmission (n = 71)	Drugs Never Approved During Study (n = 80)	*P* Value
Efficacy deficiencies only	48 (31.8)	15 (21.1)	33 (41.3)	.01
Safety and efficacy deficiencies	41 (27.2)	13 (18.3)	28 (35.0)	.03
Safety deficiencies only	39 (25.8)	24 (33.8)	15 (18.8)	.04
CMC alone	17 (11.3)	13 (18.3)	4 (5.0)	.02
Labeling alone	4 (2.6)	4 (5.6)	0	.05
CMC and labeling	2 (1.3)	2 (2.8)	0	.22

Source: Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012. Sacks et al, JAMA 2014

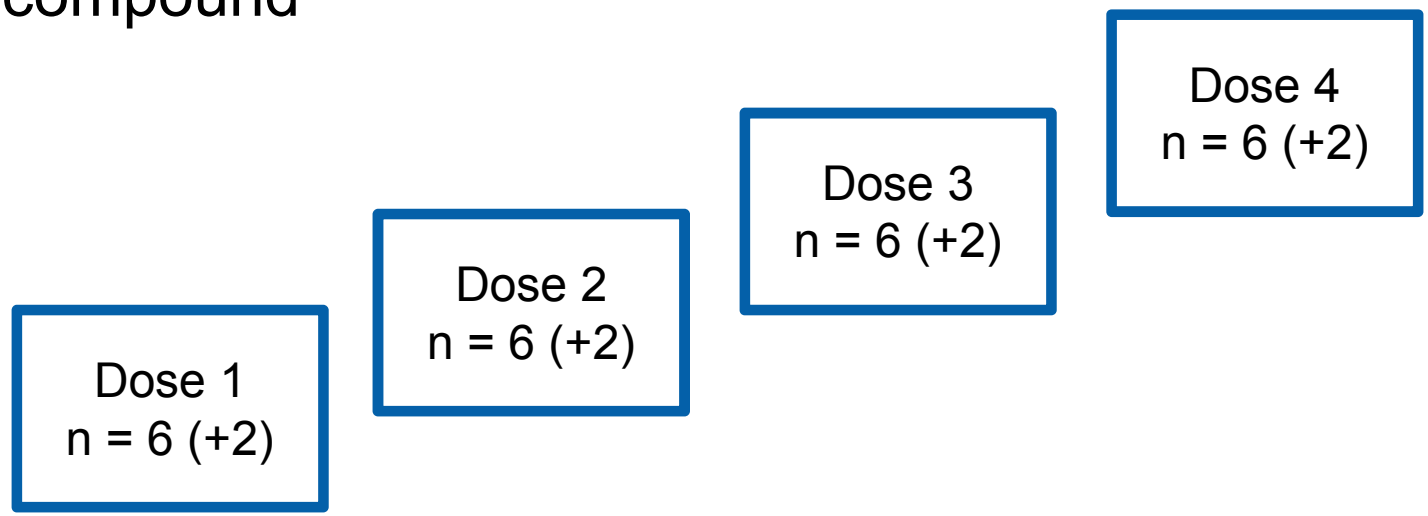
Three angles for safety in early drug development

- Toxicology studies in animals identify target organs
- Phase I dose-escalation studies in humans with primary goal to study safety
- Once safety risk is identified, Phase IIb studies determine a dose with optimal benefit-risk profile

Dose-escalation studies

Focus of safety analyses:

- Immediate safety of trial subjects
- Determination of safety profile of investigational compound



The approach we suggest for internal decision making

- Analyze continuous changes from baseline in laboratory parameters and relate them to drug exposure
- When a signal arises, put it in context with expected incidence without drug (‘virtual safety controls’)

Exposure-response analyses for safety

- Very successful in cardiac safety (QT prolongations)
- Controversial for liver safety (first-pass effect), however exposure-ALT relationships exist with many hepatotoxic compounds

Exposure-response analyses for liver safety

- Lumiracoxib: withdrawn from global markets in 2007 due to hepatotoxicity
- Dose-escalation study: 5 doses, 30 volunteers

$$\Delta\, ALT_i = \alpha + \beta * \log(AUC_i)\,, \qquad i = 1, \ldots, 30$$

- $\beta > 0$ (p=0.09)

Putting signals in context with expected incidence without drug

- Examples of signals from first-in-man studies:
  - Moderate ALT elevation (>ULN) in 1/6 healthy subjects receiving active drug
  - Moderate heart rate elevations (by >20 bpm) in 2/6 healthy subjects receiving active drug
  - Marked amylase elevation (>2 ULN) in 1/6 healthy subjects receiving active drug

Question: how likely is it that these are related to drug?

Data we can use to assess relationship to drug

- 3 desirable characteristics:
  - As close as possible to a clean control group
  - With the most amount of raw data (subject characteristics, longitudinal measurements if possible)
  - Large sample
- Internal historical studies often win over real world evidence for first 2 characteristics

Example: a subject in a first-in-man study with abnormal amylase

- 1/6 healthy volunteers treated with investigational drug presents with amylase > 2 ULN
- We have raw data from 99 historical Novartis studies in healthy volunteers where placebo has been given
- From these historical data, what is our best estimate of the probability that 1/6 subject would have amylase > 2 ULN under placebo?

Novartis healthy volunteer studies with placebo

N = 1775 subjects (99 studies)		n	%
Gender: Male		1471	82.9
Ethnicity: White		1203	67.8
Asian		287	16.2
Black		215	12.1
Native American		12	0.68
Other		58	3.27
	median	IQR	range
Age (years)	34	26-44	18-78
Height (cm)	175	168.5-181	143.8-199
Weight (kg)	77.9	69-86.4	47.7-116.1

Is 1/6 subjects with amylase>2ULN likely under placebo?

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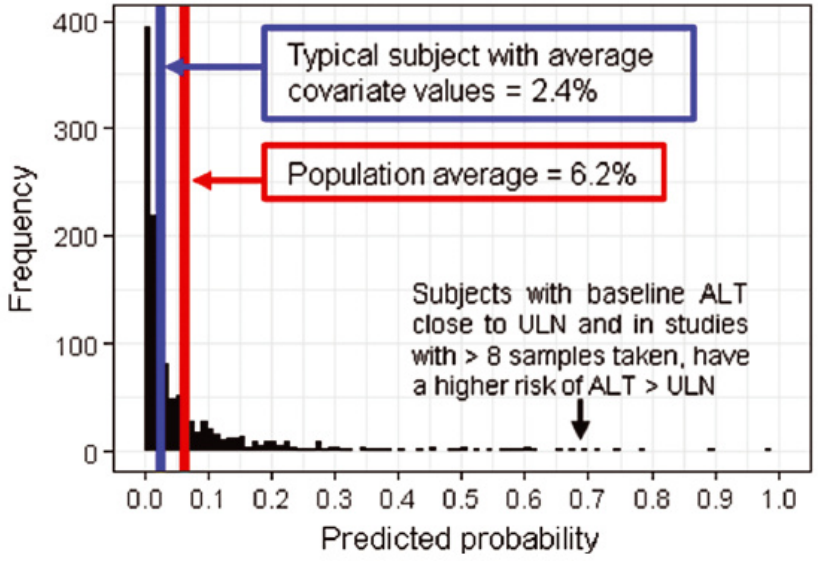
Model for probability of ALT>ULN (healthy volunteer placebo database)

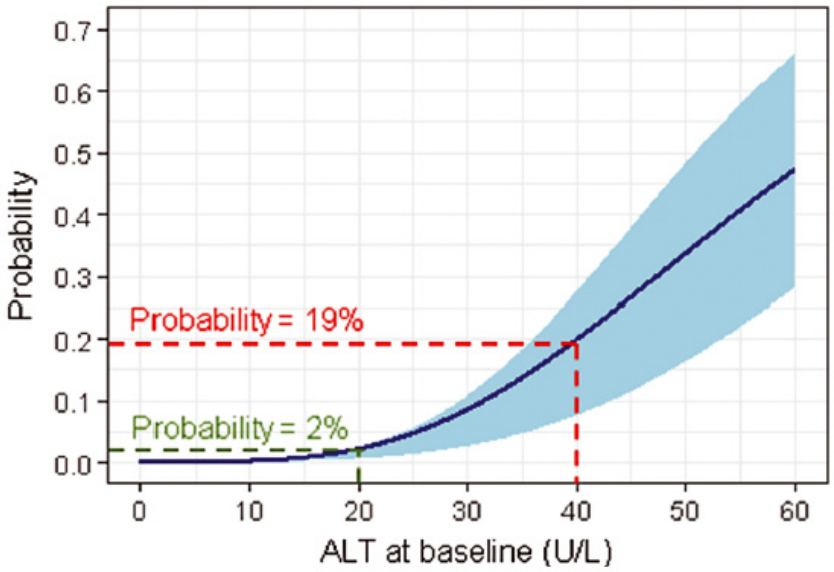
- When subject characteristics, baseline ALT, number of measurements are available, more precise answers can be given
- Probability of ALT > ULN modeled on the logistic scale
- Random effect for study
- Fixed effects: baseline ALT, age, weight, number of post-baseline samples

The risk distribution is skewed and baseline is a strong predictor

Distribution of individual predicted probabilities for ALT > ULN



Predicted probability of ALT > ULN vs. baseline ALT (U/L)



Risk prediction for each subject (had they been taking placebo)

Subject	Baseline ALT (U/L)	ULN (U/L)	Number of post-baseline samples taken	Age (years)	Weight (kg)	Predicted probability ALT>ULN under placebo
1	16	55	5	22	75	1.4%
2	21	55	5	32	78	2.9%
3	28	55	5	47	70	6.2%
4	35	55	5	25	80	15.7%
5	40	55	5	52	76	14.4%
6	50	55	5	35	77	33.9%

Nothing unusual for liver safety in this cohort

- For this cohort, the predicted probability to observe at least one ALT > ULN is 57%
- Therefore, there is nothing unusual about observing 1/6 ALT > ULN under drug

Other applications: in-licensing evaluations

- A first-in-man study with 4/44 subjects with heart rate elevations above 100 bpm (would be expected 9.8% of the time)
- A first-in-human study with 3/90 lipase elevations > 3x ULN (would be expected 1.6% of the time)

Other applications: pediatric patients in studies

- Following the PREA legislation, we are including more pediatric patients in clinical studies
- Existing reference ranges for pediatric liver parameters are not very reliable (and known to differ by age group/sex)
- Using real world evidence (claims database), we can calculate probability that an 8-year-old would present with a given lab value in the real world

Conclusions

- Using large databases, we can help quantifying the probability that a small safety signal would have happened in the absence of drug
- Statisticians have a role to play in helping their organizations quantify the level of risk in every decision:
- ‘We estimate that the events observed in the current study would have been very unlikely to happen under placebo’
- Statisticians also have a role to play in communicating the limitations of the risk assessment

References

Clayton, G. L., Schachter, A. D., Magnusson, B., Li, Y. and Colin, L. (2018), How Often Do Safety Signals Occur by Chance in First-in-Human Trials? Clinical and Translational Science.

Thank you

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