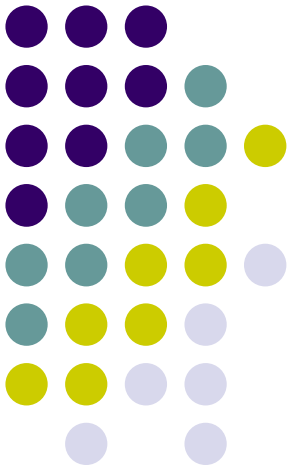
Ethical Issues for Biostatisticians

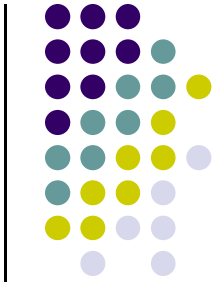
The Remune Story



Outline

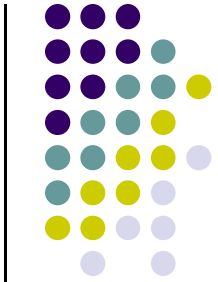
- Overview of readings:
  - Remune overview
  - Kahn study brief review
  - Churdboonchart study brief review
  - Key points of Glidden et al letter and the authors' reply
- Discussion

Remune overview



- Potential HIV therapeutic vaccine
  - Generic name: HIV-1 immunogen
  - Immune response therapy composed of inactivated HIV
  - Intended to slow disease progression
  - Conceived by Jonas Salk
  - Product of Immune Response Corporation (IRC)
- Trials (selected):
  - Kahn et al report on Study 806, a phase III trial designed to definitively assess efficacy
    - Primary endpoint (clinical): HIV progression-free survival
  - Churdboonchart et al report on a Thai phase II study designed to evaluate safety and efficacy
    - Primary endpoint (surrogate): CD4 count

Kahn et al brief review



- Timeline: March 1996, terminated early May 1999
- Phase III multi-center, double-blind, placebo-controlled, randomized
- 2,527 infected adults from 77 US centers
- Treatment:
  - Treatment: HIV-1 immunogen with incomplete Freund adjuvant (IFA)
  - Placebo: IFA, no HIV proteins
  - Injections every 12 weeks for 13 planned vaccinations
  - Additional antiretroviral therapy (ART) allowed and changes to ART permitted
- Outcome (efficacy endpoints):
  - Initially AIDS-free survival
  - Modified to HIV progression-free survival due to 1997 DSMB judgment that increased use of protease inhibitors (PI) may lead to better AIDS-free survival

Kahn et al brief review

- Primary result: No evidence of treatment differences (Figure 4)
- Supporting evidence:
  - Randomization worked (Table 1)
  - Groups were balanced in ART use (Figure 2) and in distribution of time to change of ART and PI (Figure 3)
  - No evidence of subgroup variation for the primary endpoint (Tables 2, 3)
  - Secondary endpoints and viral substudy generally but not completely supported the primary result (text p. 2199 and Figure 5)
- Conclusion:
  - Failed to demonstrate an effect on HIV progression-free survival
  - Results are “adequate to exclude a beneficial effect of HIV-1 Immunogen of the magnitude targeted when the study was designed”

Kahn et al comments

- Number of events smaller than planned due to treatment changes
  - Progression of 1.8 per 100 person-years well below experience prior to introduction of PIs
- No differences in most secondary endpoints
- Improvement in CD4 count in the treatment group (P=.02) was discounted because may not be clinically significant and the result was not adjusted for multiple comparisons
- Lack of benefit in a subset (n=435) with undetectable viral load at baseline was “particularly discouraging”
- Study allowed evaluation of benefit under unrestricted use of ARTs
  - More heterogeneous background but practical and ethical considerations made restriction of ART infeasible
- Could not detect transient effects of treatment due to infrequent assessment of intermediate markers
- Results based on incomplete data; authors conclude the likelihood that the results will change with complete data is low
- Noted the disagreement with the sponsor

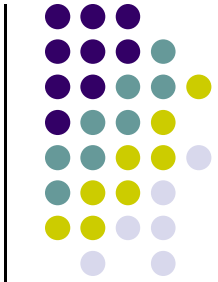
Churdboonchart et al brief review

- Timeline: Not stated
- Phase II multi-center, placebo-controlled, double-blind, randomized
- 297 infected asymptomatic Thai subjects from 5 sites
- Treatment: 2:1 randomization
  - Treatment: HIV-1 immunogen with incomplete Freund adjuvant (IFA)
  - Placebo: IFA, no HIV proteins
  - Injections every 12 weeks for 4 planned vaccinations
  - No antiretroviral therapy (ART) allowed
- Outcome:
  - Primary: Changes in CD4 cell counts
    - No details in the methods section on how this was quantified
    - Figure 1 reports mean changes by week and mean area under the curve minus baseline (AUCMB)
  - Secondary: Percent changes in CD8-cell counts; also percent CD4, CD8, CD4/CD8 and body weight. In addition HIV-1 antigen delayed-type hypersensitivity skin test (DTH) as a measure of immunity

Churdboonchart et al brief review

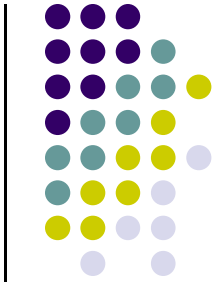
- Primary result: Strong evidence of treatment differences (Figure 1)
- Supporting evidence:
  - Randomization worked … mostly(?) (Tables 1, 2; text p. 729)
    - Groups had different numbers of CD4 and CD8 cells at baseline (unclear if these differences are meaningful)
  - Secondary endpoints (other measures, DTH skin test reaction) and viral sub-study results generally but not completely supported the primary result (Table 3, Table 4, text p. 730)
    - Most results reported at week 40
    - The only time course results appear in Figure 1
  - No differences in adverse events (Table 6)
- Conclusion:
  - "Absolute $CD4^+$ counts increased significantly without any toxicity"

Churdboonchart et al author comments



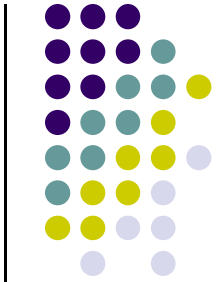
- Other research has shown CD4 counts, independent of viral load, are associated with improved HIV outcomes
- Results confirm previous studies with HIV-1 immunogen "to augment CD4-cell numbers and HIV-1-specific immune function in asymptomatic subjects not taking antiviral drug therapy"
- "Both absolute CD4-cell counts and HIV-1-specific immune function were enhanced from those at baseline in the IFA treatment group"
  - Note: Presumably "IFA treatment group" means the control group
  - Note: Could not find the evidence in the results section to support this statement
- "This trial has demonstrated that the HIV-1 immounogen can enhance CD4-cell counts and HIV-specific immunity in HIV-1-infected Thai subjects."
- "Remune is safe and signficantly increased CD4-cell counts and HIV-specific immunity …"
- "…this HIV-1-specific immune-based therapy may be an important treatment alternative in countries where access to antiviral drugs is limited."

Glidden et al letter



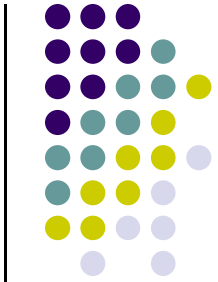
- State Churdboonchart et al “paper presents a misleading account of the study results and a distorted view of the beneficial effects of Remune in this population.”
- Full involvement: These authors are statisticians who:
  - Were involved in the study design
  - Contributed to the development of case report forms
  - Provided data management training
  - Set up the randomization and held blinded treatment codes
  - Presented to the DSMB on its role and the results of planned interim analyses. One author was a DSMB member.
  - Developed an analysis plan for the final study data
  - Conducted interim analysis
  - Prepared a final statistical report on the study results

Glidden et al letter



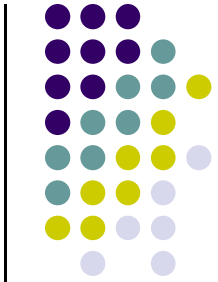
- The one primary analysis and 9 secondary analyses give different p-values (Table 1)
  - All ten were listed in the final study statistical report
  - None were adjusted for multiple testing
- The primary analysis reported by Churdboonchart et al was
  - Not primary in the written analysis plan
  - Was the most statistically significant finding (after recalculating the result using the Wilcoxon rather than the van der Waerden test)
- The final statistical report concluded the data did not demonstrate an overall difference in CD4 between groups
- Cited ASA ethical guidelines, noting the pitfalls of selective reporting and multiple testing

Churdboonchart et al reply to Glidden et al



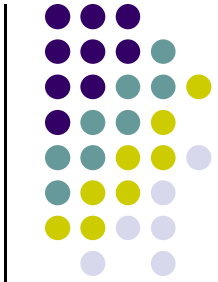
- AUC metric was selected because
  - Most common metric used to asses changes in CD4 cell counts
  - Based on a clinical hypothesis that immunization would result in increments in CD4 cell counts over time associated with immunity
  - Makes no assumptions about the distribution of the data
  - Provides a good approximation of the biological effects of immunization
  - Was used in another trial as a basis of approval of a treatment even though there was a small difference for one of two doses that was not significant for the mean or median counts
- Slope metric as the primary metric
  - Lacks a valid scientific rationale
  - Makes assumptions about data distribution which may not be valid
  - Potentially excludes important information

Churdboonchart et al reply to Glidden et al



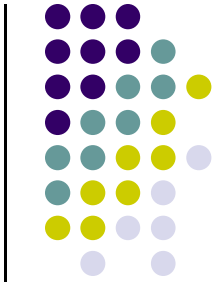
- Primary endpoint result was
  - Reviewed by all investigators
  - Presented to several Thai review committees and various AIDS conferences
  - “Considered one of the most important clinical presentations by an independent clinical rapporteur” at an international AIDS conference
  - Reported to be relevant: “statistical models which predict clinical relevance … suggest the clinical relevance of …” the observed results
- Noted
  - Trial results have been successfully reviewed by official committees
  - Remune has been approved for further clinical development in Thailand
  - Tukey’s warning that “statistics should not be “sanctified” to impede scientific progress”

Discussion questions contrasting the two scientific papers



- Which scientific paper is makes a more compelling case for its conclusions and why?
- Is there anything obviously wrong with either paper?
- What evidence of ethical problems, protocol violations, questionable practices, etc. is apparent from each of the papers?
- How do the corrections to each of the papers affect your opinions of the results and conclusions?
- Did the peer review process give you any insights into the ethical issues of the two peer-reviewed papers?

Additional discussion questions



- What is the role of journalism and other communication in the widespread understanding of this story?
  - Why is so much of the additional information (e.g. Haack article, UCSF press release, newspaper reports, stock prices) omitted from the scientific papers?
  - How do the journalistic accounts affect your opinion of the scientific findings?
- How does the use of significance testing affect
  - The arguments?
  - The appropriate inference?
- Suppose the AUC analysis reported by Churdboonchart et al was indeed the primary hypothesis. Does that affect your conclusions?
- How do the commentaries following each of the papers affect your opinions of the results and conclusions?