Non-Placebo and Add on Clinical Trials

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Present state of the Art

- All treatments are considered “empiric”
- There are no completed randomized double blind placebo controlled trials
- Retrospective review indicates empiric therapy reduces ARR
- There remains an unmet medical need

Study Designs

- **Add-on to current therapy**
  - Permits background ISTs
- **Active comparator**
  - Any comparator at any dose
  - Single specified comparator with fixed dose
  - Single medication or combination
- **Randomized withdrawal**
  - Withdraw ISTs within study
- **Historical Control group**

Add-on Trial Design

- Experimental treatment is add-on to background "empiric" therapy
  - Stable maintenance dose of any empiric therapy or combination
    - Azathioprine plus steroids
  - Fixed dose of a single specific empiric therapy
    - e.g. Azathioprine
  - Specific empiric therapy with no dose restriction

Add-on Trial Design

Pros:

- May reduce risk of relapse by allowing empiric therapy in the placebo arm
- No need to withdraw current therapy
- Establishes that the treatment is better than present treatments
- Defines the treatment effect of empiric therapy in the placebo arm

Add-on Trial Design

Cons:

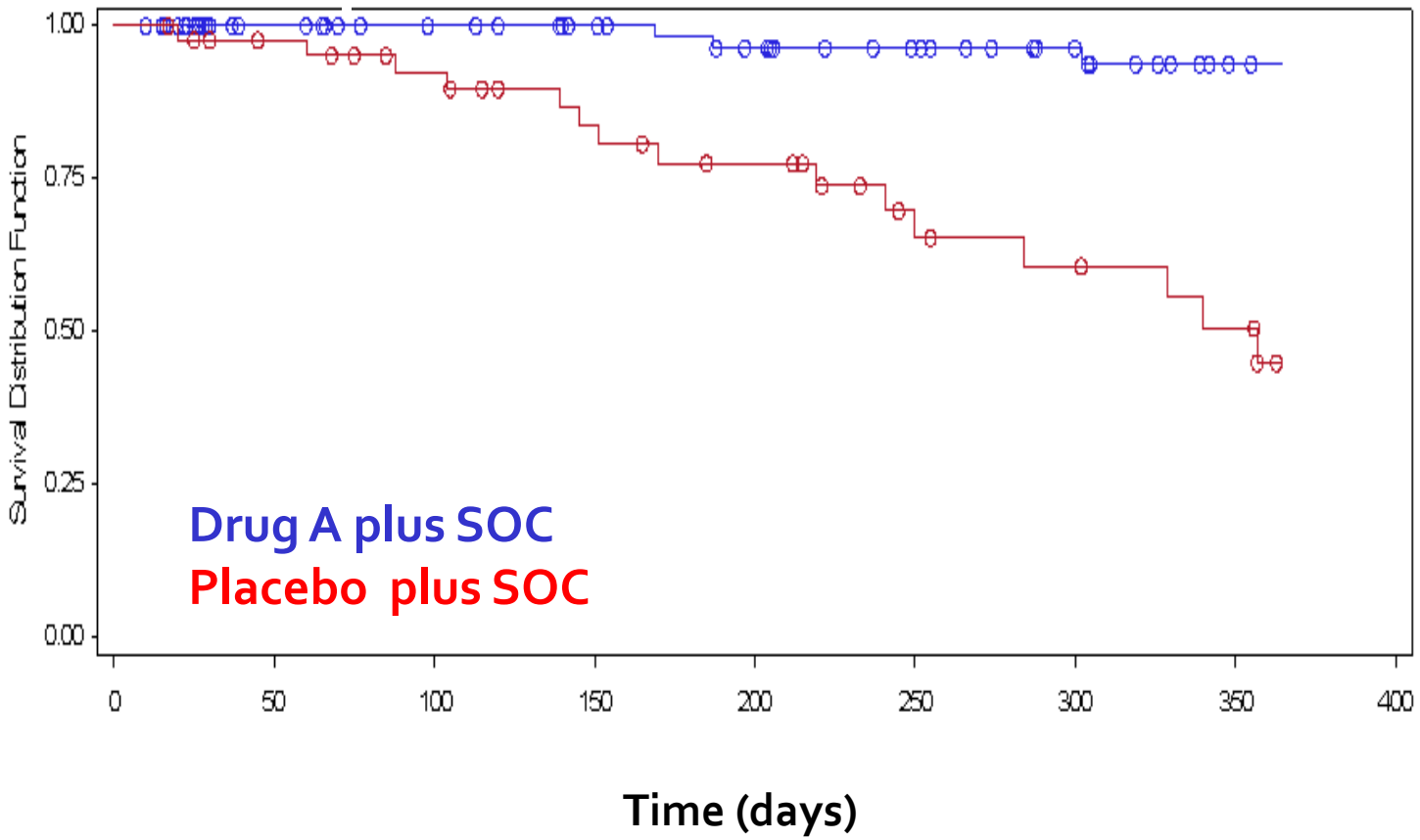
- "Unwarranted attribution of benefit to combined treatment"
- May be difficult to establish the treatment effect of the new therapy if it is not robust
- Patients may have already failed several empiric therapies
  - Enrollment issues and restarting prior failed medication
- May increase the number of attacks needed to show efficacy compared to a placebo only design
- Additional safety risk

Add-on Trial Design

Efficacy Assessment:

- Can the effect of the new treatment be clearly defined?
- Is the treatment effect dependent on the presence of other treatments?
- Is the treatment effect only present with one type of concomitant medication?
- Is there an additive treatment effect?

Time to first Relapse

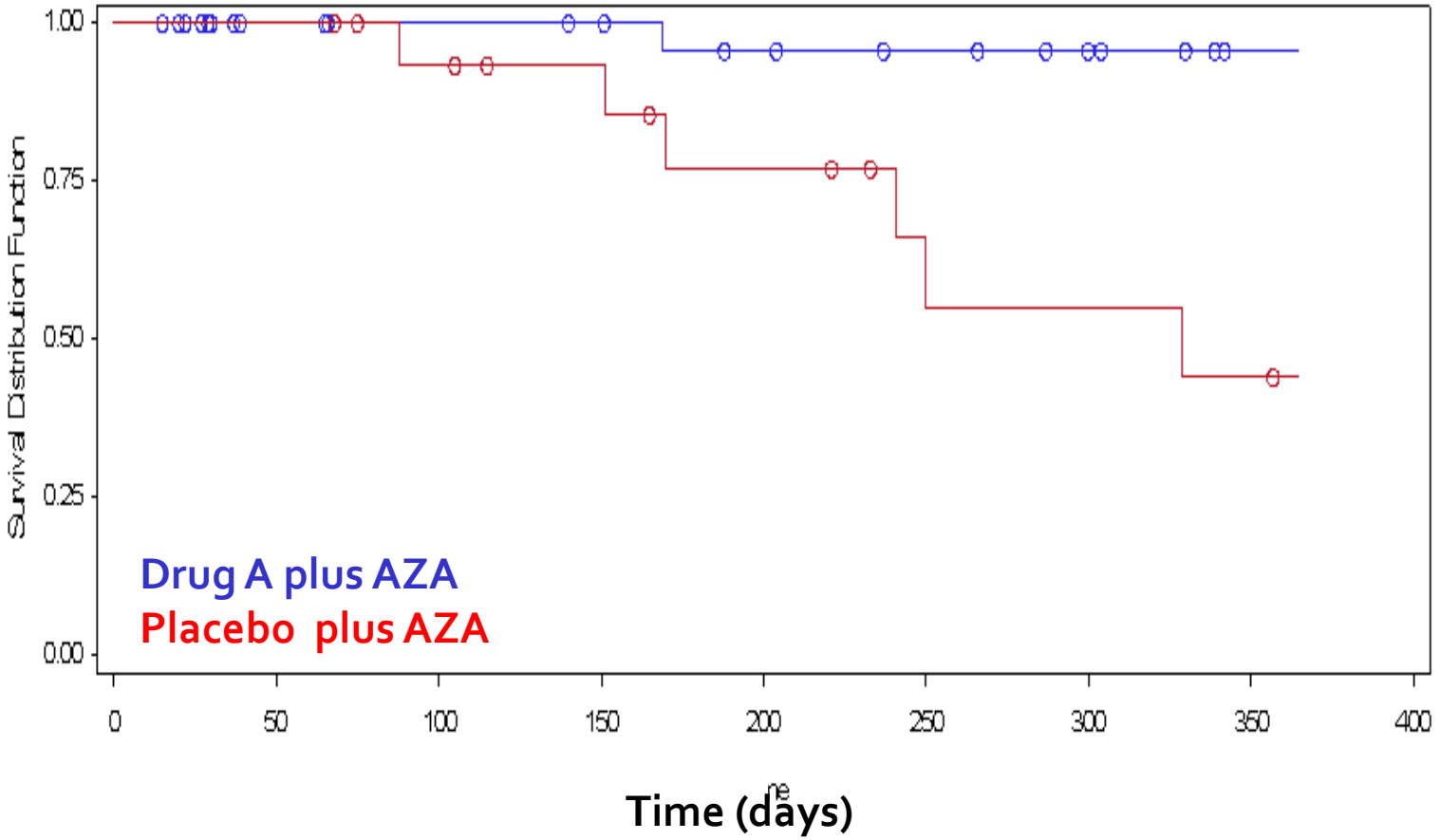


Add-on Therapy

Sensitivity analysis

- Compare subgroups
  - For each empiric therapy
    - i.e. AZA +A vs AZA + placebo
    - For combinations of empiric therapies
- If treatment effect is robust sensitivity analyses have the potential to determine if the effect is due to the combination or is independent
- Group size may limit interpretation due power considerations

Time to first Relapse



Add-on Trial Design

Safety Assessment :Additive toxicity

- Related to MOA of both treatments and off target toxicity
- May require more robust safety monitoring
- Pharmacokinetic and Pharmacodynamic interactions

- Mitigated by
  - Understanding the safety profile of both agents
  - Enhanced safety monitoring
  - Defining adverse events of special interest
  - Unblinded safety review by DMC
  - Assessment of PK and PD with other treatments

Comparator Trial Design

Why compare to an unproven therapy ?

- Comparator must be established to be better than placebo
  - There is no comparator that meets this criteria
- Superiority trial needed
- Annualized relapse rates are not firmly established for empiric therapies
- Only compares to one treatment regiment : regional differences
- Worsening caused by one therapy may be interpreted as efficacy of the other treatment

Withdrawal Trial Design

- Initiate treatment with experimental compound as add on to existing therapy
- Active and Placebo groups
  - Stable background treatment
  - Prescribed stable background treatment of single medication
  - Combination treatments
- Withdraw empiric therapy at specified time ,over specified time interval

Withdrawal Trial Design

- **Pros**
  - Mechanism to withdraw in a controlled manner
- **Cons**
  - Unclear how long the effect of empiric therapy persists
  - May place both groups at risk of relapse
    - Due to withdrawal
  - What is the risk of relapse in this clinical scenario
    - No data to power study

Historical Control Trial Design

- The understanding of Neuromyelitis Optica has evolved significantly
- Discovery of AQ4P antibody
- Time to diagnosis has shortened dramatically
  - 12.4 years prior to 2004 to 0.1 years 2009 *
- New Diagnostic Criteria have been proposed several times since 1999
- Some prior empiric treatments are now known to be detrimental

* Tackley G et. al. ECTRIMS 2014

Historical Controls

- Defining the appropriate historical control group would be difficult
- Need to match on several characteristics
  - Gender
  - Race
  - Age of onset of first attack
  - Serotype
  - Onset attack phenotype (i.e. type of onset attack)
  - Untreated ARR
  - Regional standards of care

Placebo Only Trial Design

Active drug vs. Placebo only

- Cleanest Design
- There are risks to the patient
  - What is the incidence of relapse in this clinical scenario
- Enrollment may be difficult
- Mitigation strategies to reduce risk are not adequate
  - Reducing time on placebo
    - Increases total number of relapses
  - Liberal escape clause

Placebo Only Trials

- Recent data show attacks off treatment are more likely to result in significant deficits

Transverse Myelitis	Off Treatment	On Treatment	
	n=24	n=12	
Change in EDMUS score mean(SD)	3 (3.17)	0.21 (3.12)	P< 0.05
% no residual change	33.3	50	

* Tackley G et. al. ECTRIMS 2014

Add-on Study Trial Design

- Offers some degree of protection against relapse to the placebo treated patients
  - SOC
- Permits comparison to empiric therapies not just placebo
- No need to withdraw relapsing patients from current therapy
- If the treatment effect is robust , transformative
  - Sensitivity analyses have the potential to determine if the effect is due to the combination or is independent
- Patients may see this option as more acceptable

QUESTIONS