Selection of Control Groups for PML Clinical Trials

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Disclosures

- I have no relevant disclosures

Introduction

PML presents several challenges for trial design

- PML has an annual estimated incidence of 1 in 200,000 people
- There appear to be distinct PML populations
- PML occurs because of immunosuppression
- There are no approved therapies for PML

Purpose of Control Groups

- “Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment.”

Types of Control Groups

- Concurrently Controlled Groups
  - placebo
  - no treatment
  - different dose or regimen of the study treatment
  - a different active treatment
- External (historical) control groups

Concurrent Control Groups in PML Trials

- Placebo control remains “the gold standard”
- Trials +/- immune modulation therapies?
  - Add-on trials are placebo-controlled trials
- Defining current “standard of care”
  - Many therapies in use without trials demonstrating evidence of efficacy and safety

Rare Disease Use of Historical Controls

- Unmet medical need
- Well-documented, highly predictable disease course that can be objectively measured and verified
- Expected drug effect that is large, self-evident, and temporally closely associated with the intervention

Rare Diseases: Common Issues in Drug Development Guidance for Industry

General Concerns with Historical Controls

- Serious concerns about the ability of such trials to ensure comparability of test and control groups and their ability to minimize important biases

- Even diseases with a highly predictable clinical course and an objectively verifiable outcome measure may have important prognostic covariates that are either unknown or unrecorded in the historical data

Concerns with Historical Controls in PML

- External control databases are limited
- Different databases may be needed based on representations of underlying etiologies
- Evolution in treatment and outcomes based on when data were acquired

Example of Handling Standard of Care

- NMOSD is a rare, potentially fatal autoimmune disease

- Stakeholders suggested that trials without "standard of care" treatments would not be practicable and would not enroll

Soliris (eculizumab)

- Approved for NMOSD June 27, 2019, based on results from a single double-blind placebo-controlled trial which enrolled 137 patients total and yielded a significant ($p<0.0001$) 94% relative reduction in risk of relapse associated with treatment

- Trial allowed concurrent immunosuppressant therapy (IST) status (treatment naïve, continuing the same IST since last relapse, or changed/added IST since last relapse) and allowed enrolled patients to continue treatment with specified ISTs provided that the dose had been stable prior to randomization and remained stable throughout the blinded treatment period

IST at randomization	Eculizumab		Placebo	
	n=96	%	n=47	%
corticosteroids alone	16	16.7%	11	23.4%
Azathioprine	37	38.5%	13	27.7%
Azathioprine alone	8	8.3%	6	12.8%
Azathioprine with corticosteroids	29	30.2%	7	14.9%
Mycophenolate mofetil	17	17.7%	8	17.0%
Mycophenolate mofetil alone	10	10.4%	5	10.6%
Mycophenolate mofetil with corticosteroids	7	7.3%	3	6.4%
Other ISTs	5	5.2%	2	4.3%
Other ISTs alone	1	1.0%	0	0.0%
Other ISTs plus corticosteroids	4	4.2%	2	4.3%
No IST use at randomization	21	21.9%	13	27.7%

Source: Clinical Review for Soliris (eculizumab)

Enspryng (satralizumab-mwge)

- Approved for NMOSD August 14, 2020, based on results from a two double-blind placebo-controlled trials

- The protocol of one of two trials supporting approval allowed adult patients to remain on concurrent baseline immunosuppressive treatment with azathioprine, mycophenolate mofetil, or oral corticosteroids

Table 5 Efficacy Results from Study 1 and Study 2 in anti-AQP4 Antibody Positive NMOSD Patients

	Study 1		Study 2	
	ENSPRYNG N=41	Placebo N=23	ENSPRYNG + IST* N= 26	Placebo + IST N=26
Time to Clinical Endpoint Committee (CEC)-Determined Relapse (Primary Efficacy Endpoint)				
Number (%) of Patients with Relapse	9 (22)	13 (56.5)	3 (11.5)	11 (42.3)
Hazard Ratio (95% CI)	0.26 (0.11, 0.63)		0.22 (0.06, 0.82)	
p-value	0.0014		0.0143	
Risk Reduction	74%		78%	
Proportion of Protocol Defined Relapse-Free Patients at 96 Weeks	76.5%	41.1%	91.1%	56.8%

* IST = immunosuppressant therapy

Source: Prescribing Information for Enspryng (satralizumab)

Summary Conclusions (1)

- As a rare, potentially fatal disease, PML represents a challenging disease for trial design

- The utility of historical data appears limited but can inform trial design and choices of efficacy outcomes

Summary Conclusions (2)

- Inclusion of reasonable (but unproven) concurrent therapies into prospective clinical trials can be a potentially acceptable trial design feature

- The ultimate goals for all stakeholders are high-quality trials designed to yield clinically relevant and interpretable outcomes


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