Regulatory Workshop on Clinical Trials Designs in Neuromyelitis Optica and Spectrum Disorders

EU clinical view

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The disease, the patients and their treatments

Where are we?

What are the questions we want to answer with trials on NMOSD?

EU neurologists view

Potential consequences a placebo-control trial in NMOSD

Past and current evidence

- Even prior to the discovery of AQP4-Abs, it was clear to those treating NMOSD patients that immunosuppr was beneficial in the prevention of further attacks
- Subsequent (mainly retrospective) studies showed clearly that immunosuppr medications prevent attacks in this potentially devastating disease mediated by AQP4-Abs
- Small open label studies (e.g. rituximab and eculizumab) and a (unpublished) retrospective analysis showed that immunosuppr medications not only prevent attacks, but may also reduce their severity

Attacks can be devastating, with a high risk of morbidity and mortality

It is vital that we aim for no relapses using the best available treatments

Vast consensus on early and continuous preventive treatment

- It is standard of care in great majority of centres worldwide that patients with a first episode of AQP4-Ab mediated disease are offered chronic immunotherapy due to their high risk of relapse

But if the current immunosuppressive treatments fail?

- The drugs under investigation may potentially be very valuable in patients that fail to respond to other treatments

- Will these new drugs *be superior and safer* than current immunotherapies that we already know help control disease activity in NMOSD patients?

Unfortunately, a placebo-control trial, will not answer the question of superiority of efficacy

- The trial will simply tell us whether a certain new drug is better than no drug
- It is virtually guaranteed that any immunosuppression will be more effective than doing nothing at all

And

- Is it superior to the current treatments?

EU survey
19/30 answered

- 9 countries
  - Austria, Denmark, France, Germany, Poland, Portugal, Spain, Turkey, UK
- 11 manage only adults; 3 only children; 5 both
- All 19 responded to all questions
- 6 added small comments
- 1 added a message to the EMA regulators

EU survey

All 19 responders manage patients with AQP4-Ab mediated disease

	YES	NO	May be	Sometimes
Q1 Do you treat all the AQP4 positive patients chronically from the time of diagnosis with any form of standard immunosuppression?	18			1
Q2 Do you feel that there is enough clinical evidence for the use of the standard immunosuppressive medication in NMOSD?	15	3	1*	

*Some observational evidence (not from pragmatic clinical trials)

EU survey

	YES	NO	May be	Sometimes
Q3 Based in your experience and /or knowledge, do you agree that a proportion (~15-20%) of patients respond poorly to the standard preventive treatments ?	19			
Q4 When patients fail to respond to standard immunosuppressive prophylactic treatment (breakthrough), do you usually change medication or doses to prevent more effectively further attacks?	18		1	
Q5 And would you agree with the clinical view that those patients (mentioned in Q4) need to be considered to change to a different treatment; i.e. would be candidates to a new immune medication?	19			

EU survey

	YES	NO	May be	Sometimes
Q6 Would you sign up to a clinical trial where patients with active disease/fail to respond to standard care are randomised to be in a placebo-control trial comparing active agent vs no treatment?	3*	16		
Q7 Do you agree that we should now be looking for immune treatments that are superior to the standard ones, and, therefore, clinical trials that compare new agents with standard ones?	19**			

*Yes, under a well defined ethical statement

**Placebo RCT add on would be the trial design to consider

EU clinical view

- Great majority of EU neurologists surveyed would not sign to enroll patients in a drug trial for NMOSD with a placebo only arm
- All agree that the key question is about the potential superiority of new agents over the current standard of care

It is important to make clear to the EMA regulators

- Early initiation of attack preventive medications is crucial to prevent accumulation of disability
- There is evidence for efficacy of immunosuppr therapy in attack prevention (experience and peer reviewed publications)

- *There is need for superior immune therapies – more effective and safe*

Also

Currently, there are no established markers to predict

- time to next relapse
- relapse severity
- relapse outcome

And those uncertainties would contribute to increase the clinical vulnerability of patients in a placebo only arm

Final thoughts

- As it has been happening in other autoimmune or inflammatory diseases (e.g. SLE, GCA) and in transplantation
  - Transfer evidence from similar diseases
  - New treatments are compared with standard of care (add on design)