Immediate versus deferred anti-epileptic drug treatment for early epilepsy and single seizures: a randomized controlled trial.

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At the time of this trial, the timing of anti-seizure medication (ASM) initiation following a first-time seizure was unclear, as there was relatively little data on the risk/benefit to early ASM initiation. Seizure recurrence after a first-time event had been reported to be between 23 - 71%, and up to 50% of patients with first-time seizures were without seizure recurrence (if in the absence of EEG or MRI abnormalities). Despite this, basic science research had suggested that epilepsy was a self-perpetuating process that might warrant early treatment and prevention, though the effects of early ASM treatment on the natural history of epilepsy had not been well-studied. As such, the goal of this trial was to assess the risk/benefit of immediate vs. delayed ASM treatment following a first-time seizure on seizure recurrence, longer-term outcomes, and quality of life.

Experimental design and statistics: This was a multicenter, unmasked, randomized controlled trial, with eligible patients including those > 1 month of age, an adequately documented history of a single, spontaneous and unprovoked seizure. Exclusion criteria included prior longer-term treatment with any ASM (excluding prophylactic treatment or acute, single dose treatment for seizures) and progressive disease. Eligible patients were randomized to one of two treatment arms: immediate (defined as "as soon as possible") vs. deferred (when decided upon by the clinician/patient) ASM treatment. The choice of ASM was left to the participating providers. All enrolled patients obtained an EEG and MRI/CT head, and serial follow ups occurred at 3, 6, and 12 months post-randomization, then yearly thereafter. At follow ups, information regarding seizure occurrence, ASM treatment, and ASM side effects was taken. Primary outcomes were seizure outcomes, including time from randomization to 1) first seizure of any type, 2) first GTC-type seizure, 3) 2^{nd} and 5^{th} seizures, and 4) proportion of patients who were seizure-free at 2yrs. Secondary outcomes included ASM side effects and QOL scores. Statistically, to assess the time to each outcome event, Cox proportional hazard models with log-rank tests were used and data were stratified by number of reported seizures prior to randomization.

Results: A total of 1443 patients were randomized into either immediate (n = 722) vs deferred (n = 721) ASM therapy. Baseline characteristics between the two treatment groups were generally similar (Table 1). In the immediate treatment group, most providers opted to start either carbamazepine (46%) or valproate (46%), with a similar pattern noted in the deferred treatment group. Overall, a total of 48% (n=693) of those who were randomized (in total) had a seizure during follow up, with more occurring in the deferred treatment group: 43% (n=311) occurred in the immediate and 53% (n=382) in the deferred treatment group, with an HR of 1.4 ($p<0.001$, Figure 2). The pattern of results was similar for time to first GTC-type seizure (HR: 1.5, $p<0.001$) and time to 2^{nd} seizure (HR: 1.3, $p<0.001$), but not time to 5^{th} seizure (Table 2). Regarding seizure remission, more patients in the immediate group obtained 2yr remission by 2yrs in the immediate (64%) vs. deferred (52%) group ($p=0.023$), though this difference diminished over time, with converging curves by 6yrs after randomization. Similarly, at subsequent follow ups, 74% of the immediate and 71% of the deferred treatment groups were seizure free from years 1-3 post randomization, and 76% of the immediate vs. 77% of the deferred treatment groups were seizure free from years 3-5 post randomization. In terms of adverse events, the numbers of individuals who experienced status epilepticus post-randomization was generally similar between both groups, and the reported ASEs of ASMs at follow up were also similar (see Table 3). Finally, in terms of QOL data, no significant differences between treatment groups were reported (including # of patients who left and then returned to work due to their seizures).

Conclusions: Overall, this study suggested that although immediate treatment with an ASM following a first-time seizure lengthens the time it takes to experience a second event and increases the likelihood of seizure-freedom at 2yrs, immediate treatment has little effect on longer term seizure outcome: seizure remission rates were similar in both treatment groups by ~6yrs post-randomization, suggesting that eventual epileptogenesis does not seem to be affected by early vs. delayed ASM treatment. Notably, though scores of QOL were generally similar between the two treatment groups, more patients in the immediate treatment group also reported treatment-related adverse events, suggesting that longer ASM treatment is not entirely benign. Ultimately, though the study authors endorse some limitations to the study, their outcomes suggest that delaying ASM therapy following an initial seizure, at least until a second event, is appropriate and safe.

Summary created by Elaine Sinclair, D.O.