The trials and tribulations of ADAPT

ADAPT: **Alzheimer's Disease Anti-inflammatory Prevention Trial**

Alzheimer's Disease (AD) was the 8th leading cause of death in the U.S. in 2000; accounting for 49,558 deaths in that year. Worldwide, the number of people with AD in 2006 was estimated to be 26.6 million. That number is projected to grow fourfold by 2050. In the U.S. the projection is 4.58 million by 2047.

It took three tries to get ADAPT funded (all funding requests submitted to the National Institute on Aging of the NIH).

First application submitted 30 May 1997; rejected. Second application submitted 13 February 1998; rejected. Third application submitted 1 March 1999; accepted.

First person enrolled: 8 March 2000.

The trials and tribulations of ADAPT

The impetus for ADAPT was driven by data suggesting NSAIDs (nonsteroidal anti-inflammatory drugs) may reduce the incidence of AD. By the time the trial was funded, NSAIDs capable of inhibiting activity of the COX-2 (cyclooxygenase-2) enzyme – an enzyme responsible for pain and inflammation – were available.

The treatments tested, both COX-2 inhibitors, were:

Naproxen sodium (Nap); Aleve®; Bayer.	220 mg b.i.d.
Celecoxib (Cel); Celebrex®; Pfizer	200 mg b.i.d.
Placebo (Plbo); pills from Bayer & Pfizer matching Nap & Cel	b.i.d.

The trial was randomized, double masked so neither persons enrolled nor treaters knew what treatment was administered, and placebo-controlled. Randomizations were by clinic and by age group within clinic. The assignment ratio was: 1:1:1.5 (Cel:Nap:Plbo); more in the placebo-assigned group; need for increased number because Plbo was comparator for both test-treated groups.

ADAPT had six study clinics (Baltimore, Boston, Rochester (NY), Seattle, Sun City (Az), and Tampa), a Coordinating Center in Baltimore (headed by me), and Office of the Chair (John Breitner; Baltimore thru Feb 2002, then Seattle).

Things proceeded normally until 4 September 2002 when we received a letter from Sidney Wolfe, director of Public Citizen's Health Research Group (a consumer and health advocacy lobbying organization) charging that ADAPT was unethical and that it should be shut down. The complaint read in part:

The fact that there is no longer any biological basis for this trial, which is at the same time putting healthy elderly people at risk for a multitude of adverse reactions, provides the basis for our request that it be immediately terminated. This is reinforced by the failure to inform patients even of those risks mentioned in the FDA-approved labeling. The ADAPT trial should be stopped with the current 1000 patients (out of a planned total of 2625) and the patients enrolled should be fully informed about the extremely unlikely probability of efficacy of these two NSAIDs as well as the properties of these drugs that might put volunteers at risk of serious adverse reactions. There is no justification for continuation.

The trials and tribulations of ADAPT

The substance of the petition was:

1. That the hypothesis underlying ADAPT was passe,
2. That consent documents in ADAPT were "extraordinarily incomplete and misleading",
3. That the choice of study drugs was heavily influenced by pharmaceutical companies,

and

4. That ADAPT promotion and recruiting policies were "suspect".

The response from ADAPT, dated 27 September 2002 to the Secretary of Health and Human Services, was pointed and detailed.

The request from Wolfe was denied by the NIH, but there were rougher waters ahead. They started two years later when Merck announced (30 September 2004) withdrawal of rofecoxib (Vioxx®) because a trial of the product showed patients taking the drug had twice the risk of heart attacks as compared to patients receiving placebo. The decision prompted a letter from ADAPT to participants informing them of the withdrawal and that though the drug was not used in ADAPT it was a member of the class of drugs being tested in ADAPT.

On Friday 17 December 2004 I was informed by telephone by a representative of Pfizer that it was going to announce later that day that a trial of celecoxib for prevention of colon polyps was being stopped because of excess cardiovascular risk in the celecoxib-assigned group.

That information prompted a conference call later that day with the ADAPT steering committee. The committee, during the call, voted to suspend treatments in ADAPT pending further review. The option of suspending the celecoxib treatment and continuing the naproxen treatment and its placebo was considered but rejected, because doing so would have required unmasking treatment assignments. Investigators voted to make the suspension permanent 31 March 2004.

The trials and tribulations of ADAPT

Enrollment when the suspension was imposed 17 Dec 2004 was:

Nap.	719
Cel .	726
Plbo.	1,083
Total.	**2,528**

Once investigators voted to make the suspension of treatment permanent, they set about preparing a paper summarizing the cardiovascular data accumulated in ADAPT. But here the record was no better than for Vincent "Vinny" Gambini in My Cousin Vinny. He need six tries to pass the bar exam and that is what we need to get results published, proving again that editors like positive results better than nil or negative results.

Results were finally published just short of two years after suspension of enrollment.

Submission history

New Engl J Med: submitted 5 May 2005; rejected 25 May 2005

JAMA: submitted 13 Oct 2005; rejected 9 Nov 2005

Arch Int Med: submitted 21 Nov 2005; rejected 1 Dec 2005

Lancet: submitted 22 Dec 2005; revision requested 16 Jan 2006; submitted 2 Feb 2006; rejected 20 Mar 2006

Br Med J: submitted 30 Apr 2006; rejected 18 May 2006

PLOS Clinical Trials: submitted 25 Jun 2006; revision requested 25 Jul 2006; submitted 15 Aug 2006; 2nd revision requested 5 Sep 2006; submitted 11 Sep 2006; accepted 29 Sep 2006. *ADAPT Research Group: Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)*. PLoS Clin Trials 1(7):e33, **2006**.

The trials and tribulations of ADAPT

Other publications

Lyketsos CG, Breitner JCS, Green RC, Martin BK, Meinert C, Piantadosi S, Sabbagh M: Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 68:1-1, **2007**.

ADAPT Research Group, Curtis L Meinert, Lee D McCaffery, John CS Breitner: Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): Design, methods, and baseline results. Alzheimers Dement. **2009** Mar; 5(2): 93–104. doi: 10.1016/j.jalz.2008.09.004