First Transdermal Treatment for Alzheimer's Disease: Results of the IDEAL Trial

George Grossberg, MD, St. Louis University, presented data from the Investigation of Transdermal Exelon in Alzheimer's disease (IDEAL) trial. Rivastigmine (Exelon) is an acetylcholinesterase inhibitor approved for the treatment of mild to moderate dementia in both Alzheimer's disease (AD) and Parkinson's disease. Rivastigmine is currently available in capsule formulation, and its pharmacological characteristics are compatible with transdermal delivery. Advantages associated with transdermal therapy include better compliance, greater consistency in plasma levels of drug, and a decrease in time to maximal therapeutic concentrations (Cevc G. *Expert Opin Investig Drugs* 1997;6:1887-1937). The IDEAL study was conducted to determine whether the efficacy and safety of a transdermal formulation of rivastigmine would be equivalent to the oral formulation, and to collect long-term safety data.

Patients aged 50-85 with a diagnosis of AD were included in the trial, which consisted of a 24-week randomized, double-blind, placebo-controlled phase, followed by a 28-week open-label extension phase (Figure 1). The primary efficacy measures were the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of

Figure 1. IDEAL Study Design.

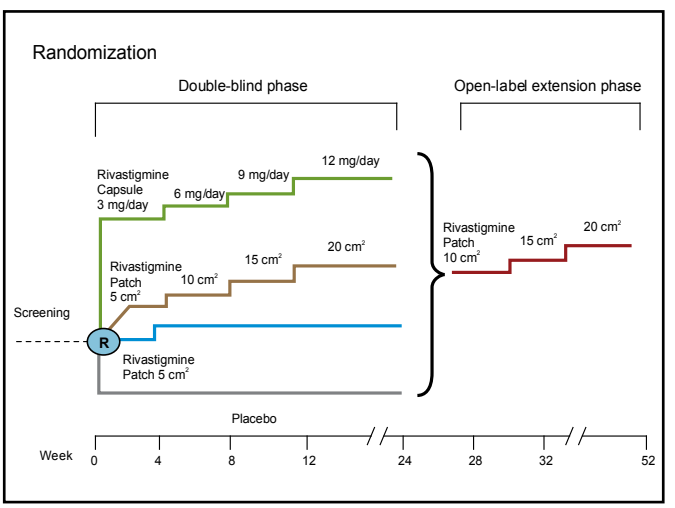

Table 1. Most Frequently Reported Adverse Events (n, %) During the Double-Blind Phase and During the First Four Weeks of the Open-Label Extension Phase Presented by the Patient's Double-Blind Phase Treatment Group.

Adverse Event	Double-blind phase treatment group			
	10 cm² patch	20 cm² patch	Capsule	Placebo
	Double-blind phase (Weeks 1-24)			
	n=291	n=303	n=294	n=302
Any AE	147 (50.5)	200 (66.0)*	186 (63.3)*	139 (46.0)
Nausea	21 (7.2)	64 (21.1)*	68 (23.1)*	15 (5.0)
Vomiting	18 (6.2)	57 (18.8)*	50 (17.0)*	10 (3.3)
Diarrhea	18 (6.2)	31 (10.2)*	16 (5.4)	10 (3.3)
	Open-label extension titration phase (Weeks 25-28) following direct switch to 10 cm² patch			
	10 cm² → 10 cm² †	20 cm² → 10 cm² †	Capsule→ 10 cm² †	Placebo → 10 cm² †
	n=204	n=209	n=209	n=248
Any AE	31 (15.2)	31 (14.8)	30 (14.4)	70 (28.2)
Nausea	5 (2.5)	4 (9.1)	5 (2.4)	21 (8.5)
Vomiting	3 (1.5)	1 (0.5)	4 (1.9)	15 (6.0)
Diarrhea	2 (1.0)	1 (0.5)	3 (1.4)	6 (2.4)

Safety populations

*p≤0.05 vs placebo

† Indicates the switch from double-blind phase treatment group (10 cm², 20 cm², capsule or placebo) to 10 cm² patch upon entering open-label extension

Change (ADCS-CGIC). Skin irritation and patch adhesions were systematically assessed.

A total of 1,195 patients were randomized to treatment in the double-blind phase, with 970 (81%) completing all 24 weeks; 870 (73%) patients continued into the open-label phase. During the double-blind phase of the study, 83.8% of patients in the 10 cm^2 patch group met the target dose of study drug for ≥8 weeks, compared to 49.5% of the capsule group and 53.1% of the 20mg^2 groups. At the end of the 24-week double-blind phase, the rivastigmine 10 cm^2 patch, 20 cm^2 patch, and capsule treatment groups were significantly better than placebo in ADAS-cog, ADCS-Activities of Daily Living scale, Mini-Mental Status Exam, Trail Making Test A, and ADCS-CGIC (all $p<0.05$), with the exception of the 20 cm^2 patch in the ADCS-CGIC ($p=0.054$). During the open-label phase, 72.6% of participants achieved the target 20 cm^2 patch. At the end of the open-label phase, patients who received rivastigmine in any form during the double-blind treatment period had small declines in the ADAS-cog when compared to baseline (-0.3); those taking placebo in the double-blind phase had a -0.9 change in ADA-cog scores compared to baseline. The most common adverse events associated with rivastigmine were nausea, vomiting, and diarrhea; The 10 cm^2 rivastigmine patch had 3 times fewer nausea and vomiting adverse events compared to rivastigmine capsule (Table 1). The open-label phase adverse events were similar to those reported in the double-blind phase. Patients taking placebo in the double-blind phase had a higher incidence of adverse events when switched directly to the 10 mg^2 patch, suggesting that naïve patients should be titrated using a 5 cm^2 patch. Local skin irritation led to study discontinuation in 2.4% of the 10 cm^2 group and 3.7% in the 20 cm^2 group. The majority of patients (>90%) experienced "none, slight, or mild" skin irritation as their most severe skin reaction during the study. Ninety-six percent (96%) of caregivers in the 10 mg^2 group reported good adhesion over 24 hours, with the patch staying completely on or just starting to lift up at the corners. The conclusion of the study was that transdermal rivastigmine treatment over one year was a convenient, effective, and well-tolerated medication delivery method in patients with AD.

Agomelatine Demonstrates Broad Efficacy in Depression

Agomelatine, a melatonergic agonist and a selective 5-HT2c antagonist, is a novel antidepressant in development for major depressive disorder (MDD). Alan F. Schatzberg, MD, Stanford University, presented a meta-analysis of pooled data from three clinical studies. The objective of the meta-analysis was to determine whether gender or baseline severity of depression had any influence on agomelatine efficacy.

The three studies included in this exercise were an 8-week dose-finding study comparing 1 mg, 5 mg or 25 mg of agomelatine, placebo, and 20 mg paroxetine and two 6-week flexible dose trials of 25-50 mg agomelatine vs placebo. In the flexible dose trials, agomelatine was increased from 25 mg/day to 50 mg/day if there was no change in Hamilton Depression Rating Scale (HAM-D) at week 2**.** Eligible subjects were outpatients aged 18-65 with a DSM-IV diagnosis of MDD, a HAM-D total score ≥22, and a Clinical Global Impression severity rating of ≥4 with no comorbid conditions that would interfere with study participation. Other psychotropic medications that could confound study data were prohibited. The primary efficacy measure in all three studies was the change in total HAM-D score from baseline to the final evaluation. For purposes of the meta-analyses, "less severe" was defined as a HAM-D total score ≤ 27 (the median total baseline score), and "more severe" was defined as a HAM-D total score ≥ 27.

A total of 358 subjects received agomelatine and 363 were treated with placebo. There were no statistically significant demographic differences between treatment groups. In the meta-analysis of overall efficacy, agomelatine was significantly better than placebo ($p<0.001$). Female patients achieved a mean decline in HAM-D score of 13.5 with agomelatine vs an 11.2 decrease with placebo ($p<0.001$); male patients experienced similar reductions (-13.7 with agomelatine vs -9.9 for placebo; $p<0.001$). There were no statistically significant differences in efficacy between men and women.

In terms of efficacy and depression severity, agomelatine was significantly better than placebo in both the less severely depressed patients and