Gli inibitori delle colinesterasi possono avere un effetto disease-modifying?

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I trials farmacologici per la MA

New pharmacological strategies for treatment of Alzheimer’s disease: focus on disease modifying drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action relevant for AD</th>
<th>Phase of study</th>
<th>Result of study</th>
<th>Caveat of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>β-secretase inhibition (?)</td>
<td>3</td>
<td>Ineffective</td>
<td>Lack of biomarker</td>
</tr>
<tr>
<td>Semagacestat</td>
<td>γ-secretase inhibition</td>
<td>3</td>
<td>Premature end</td>
<td>Severe adverse drug reaction</td>
</tr>
<tr>
<td>Tarenflurbil</td>
<td>γ-secretase modulation</td>
<td>3</td>
<td>Ineffective</td>
<td>Low potency, blood-brain barrier passage</td>
</tr>
<tr>
<td>Tramiprosate</td>
<td>Inhibition of Aβ oligomerization</td>
<td>3</td>
<td>Ineffective</td>
<td></td>
</tr>
<tr>
<td>Sertindole</td>
<td>Inhibition of Aβ oligomerization</td>
<td>2</td>
<td>Ineffective</td>
<td>emarker change</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Aβ clearance</td>
<td>3</td>
<td>Ongoing</td>
<td>Vasogenic oedema, amyloid angiopathy</td>
</tr>
<tr>
<td>Solaneuzumab</td>
<td>Aβ clearance</td>
<td>3</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Inhibition of tau phosphorylation</td>
<td>2</td>
<td>Clinical improvement</td>
<td>Decrease of P-tau in CSF</td>
</tr>
<tr>
<td>Methylthioninium chloride</td>
<td>Inhibition of tau aggregation</td>
<td>2</td>
<td>Clinical improvement</td>
<td>Lack of biomarker</td>
</tr>
<tr>
<td>Nilvadipine</td>
<td>Aβ clearance</td>
<td>Open label</td>
<td>Clinical improvement</td>
<td>Lack of biomarker</td>
</tr>
<tr>
<td>Latrepirdine</td>
<td>Mitochondrial protection</td>
<td>3</td>
<td>Ineffective</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Ongoing (in association with other drugs)</td>
<td></td>
</tr>
</tbody>
</table>

L’insieme di queste variabili ha ben poco di lineare, ma è certamente una rete complessa di relazioni che si verificano simultaneamente tra le varie pathway coinvolte, in cui attori molecolari di diversa valenza giocano la propria parte per mantenere un delicato equilibrio funzionale.

Carossa V, Preda S, Mura E, Govoni S. Innovazione e terapia della malattia di Alzheimer: il punto di vista farmacologico. Psicogeriatr 2012; 1 Suppl: 34-45
A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer’s disease

- At 9 months, 2,853 patients (52.2%) had completed the study with a mean improvement from baseline of 0.5 points (± 3.0) in MMSE scores. The conditions of one-third of patients were judged not to have deteriorated at 9 months, while a subgroup of 857 patients (15.7%) had an improvement from baseline of at least 2 points on MMSE.

- During all the study period, 10.1% of patients on rivastigmine and 8.1% of those on galantamine were treated with dosages lower than the minimal effective dose.
We observed only marginal effects and despite the large number of patients enrolled, the association between drug therapy and categories of responders, based either on the MMSE or on the ADAS-Cog scale, was found to be not statistically significant.

A possible limitation of our study is the duration of follow-up (36 weeks). According to some authors, follow-up of longer than 1 year would be necessary and desirable to demonstrate the effectiveness of drug treatment in patients with AD.

At t36, most patients were taking the highest dose, although a large proportion of patients continued on a lower dose.

Finally, despite the fact that patients with AD in our study experienced less cognitive deterioration than is attributed to untreated patients with AD in the community, we did not observe any significant difference in the effects of donepezil, galantamine and rivastigmine on a variety of functional and cognitive parameters in a large number of apoE-genotyped AD patients.
AChEIs: un’efficacia modesta?


Trapanese M, et al. I dati del monitoraggio triennale sui trattamenti farmacologici per la demenza di Alzheimier (nota AIFA 85) nella Regione Emilia-Romagna. 5° Convegno ISS; Roma, 18 novembre 2011
Terapie sintomatiche o modificanti?

Terapia sintomatica
Il paziente si sente o funziona meglio dopo l’assunzione di una terapia, la quale non modifica realmente il processo che causa i sintomi.

Terapia curativa o disease-modifying
Interventi che modificano l’esito a lungo termine o la storia naturale della malattia. Essi potrebbero non migliorare i sintomi del paziente né impedirne la comparsa di nuovi, sebbene stiano già cambiando l’esito a lungo termine della malattia.

- Questa distinzione presuppone che per ogni terapia siano pienamente compresi tutti i meccanismi d’azione e che ciascuna possa essere classificata a priori come sintomatica o modificante la malattia. Questi presupposti non sono chiaramente applicabili alle attuali terapie per la malattia di Alzheimer o a quelle ancora in fase di sviluppo.


Terapie sintomatiche o modificanti?

- I farmaci attualmente approvati e quelli in fase di sviluppo per la MA non possono essere definitivamente classificati come sintomatici o modificanti la malattia.

**Table 1**

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Presumed mechanisms</th>
<th>Possible claim to disease modification?</th>
<th>Possible improvement of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active monoclonal vaccines</td>
<td>Induce clearance of beta amyloid by activating microglia and shifting amyloid out of the brain</td>
<td>Yes</td>
<td>Yes, likely</td>
</tr>
<tr>
<td>Passive immunization</td>
<td>Induce clearance of beta amyloid by binding and clearance</td>
<td>Yes</td>
<td>Yes, likely</td>
</tr>
<tr>
<td>Secretase inhibitors</td>
<td>Reduce the production of beta amyloid</td>
<td>Yes</td>
<td>If effect is complete and rapid enough</td>
</tr>
<tr>
<td>Anti-fibrillization or deposition agents</td>
<td>Reduce the polymerization and 3-D conformational changes</td>
<td>Yes</td>
<td>If effect is complete and rapid enough</td>
</tr>
<tr>
<td>Glial cell modulators</td>
<td>Induce clearance of beta amyloid and/or reduce its production and/or inflammatory response</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurotransmitter modulators</td>
<td>Counteract transmitter imbalances while creating anti-amyloid or neuroprotective effects</td>
<td>Yes</td>
<td>Yes, likely</td>
</tr>
<tr>
<td>Neuroprotective or neurotrophic agents</td>
<td>Introduce protective peptides or metabolic regulators of energy metabolism, amyloid production, or tau hyperphosphorylation</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Anti-tau drugs</td>
<td>Reduce the likelihood of tangle formation</td>
<td>Yes</td>
<td>Yes, likely</td>
</tr>
<tr>
<td>Drugs based on risk factors</td>
<td>Shift sex hormonal balance, lipid metabolism, glucose metabolism, or energy metabolism</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neutraceuticals</td>
<td>Alter oxidative mechanisms, block amyloid fibril formation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Symptomatic benefits that were seen — in global cognitive function, activities of daily living and behavior — were more modest, and alterations in disease course more limited than expected.

On the other hand, in > 2 decades of preclinical investigation, the cholinesterase inhibitors have been found to influence a number of cellular and molecular processes related to neurodegeneration, including amyloid precursor protein (APP) processing, excitotoxicity and adult neurogenesis, among others.
Donepezil: potential neuroprotective and disease-modifying effects

Considering these myriad drug effects, the question arises as to why donepezil and other cholinesterase inhibitors do not have more robust effects in clinical population.

- The time course of observation in clinical studies (over weeks to months → years or even decades).
- The functional and gross cognitive measures used to assess efficacy are too insensitive to detect brain changes that occur.
- The drug is not administered clinically at the correct dose.
- Cholinesterase inhibitors are not being administered to the clinical population that would benefit the most from their use.

Progressive cholinergic decline in Alzheimer’s Disease: consideration for treatment with donepezil 23 mg in patients with moderate to severe symptomatology

In a post hoc analysis of patients with more severe cognitive impairment (baseline MMSE, 0-16), significant differences favoring donepezil 23 mg/d were demonstrated on both the SIB and the CIBIC-plus.

Sabbagh M, Cummings J. Progressive cholinergic decline in Alzheimer’s Disease: consideration for treatment with donepezil 23 mg in patients with moderate to severe symptomatology. BMC Neurol 2011; 11: 21
In the OPTIMA study, patients with AD demonstrating functional and cognitive decline while receiving the currently approved maintenance dose of 9.5 mg/24 h rivastigmine as a patch showed additional benefit with titration to the higher-dose 13.3 mg/24 h patch.

### Quale dosaggio?

**Dosaggio finale trattamento con ChEIs iniziato al Basale**

<table>
<thead>
<tr>
<th></th>
<th>Dosaggio (mg/die)</th>
<th>Mediana (range IQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td></td>
<td>10 (5)</td>
</tr>
<tr>
<td>Galantamina</td>
<td></td>
<td>8 (8)</td>
</tr>
<tr>
<td>Rivastigmina (orale)</td>
<td></td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Rivastigmina (cerotto)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **47%**
  - 4.6 mg/24 ore
- **53%**
  - 9.5 mg/24 ore

Studio EVOLUTION (BEhaVional symptOms in Alzheimer’s disease evaLUation of paTIents treated with chOlInesterase inhibitors)
“Switching” ChEIs

- Evoluzione della gravità della demenza (MMSE)

**Punteggio medio MMSE**

- Basale: 21.0, 20.2, 19.8
- 3 Mesi: 20.2, 19.0, 17.6
- 6 Mesi: 14.3, 14.6, 14.4

- MMSE: variazione nei pazienti lievi e moderati

Studio EVOLUTION (BEhaVioral symptOms in Alzheimer’s disease evaLUation of paTIents treated with chOliNesterase inhibitors)
"Switching" ChEIs

Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology

John T O'Brien¹, Alistair Burns²,
on behalf of the BAP Dementia Consensus Group

Table 3. Summary box: Alzheimer's disease

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with cholinesterase inhibitors and memantine</td>
<td>There is type I evidence for the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease and type I evidence for memantine in moderate to severe Alzheimer's disease.</td>
<td>A</td>
</tr>
<tr>
<td>Switching between cholinesterase inhibitors</td>
<td>There is type II evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective.</td>
<td>B</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>There is type II evidence for adding memantine to a cholinesterase inhibitor, but also a negative type 1b study. Until further studies are available the benefits of combination therapy is unclear.</td>
<td>B</td>
</tr>
</tbody>
</table>
Empirical evidence of neuroprotection by dual cholinesterase inhibition in Alzheimer’s disease

Annalena Venneri, William J. McGeown and Michael F. Shanks

Clinical Neuroscience Centre and Department of Psychology, University of Hull, Cottingham Road, Hull HU6 7RX, UK

Corresponding Author: a.venneri@hull.ac.uk

Patients whose drug treatment also inhibited butyrylcholinesterase did not show the widespread cortical atrophic changes in parietotemporal regions invariably reported in untreated AD patients, and which were detectable in the subgroups treated with selective acetylcholinesterase inhibition.

One possible explanation of the variation in the pattern of brain morphometric changes seen over time in the different treatment groups is a diminution of amyloid plaque neurotoxicity due to BuChE inhibition in the rivastigmine group.

Effects of cholinesterase inhibition on brain white matter volume in Alzheimer’s disease
Annalena Venneri and Roger Lane

- Dual cholinesterase inhibition over a period of 20 weeks in patients with minimal-to-mild AD seems to reduce WM damage, compared with AChE-specific inhibition.

- These findings suggest a role for sustained BuChE and AChE inhibition in maintaining WM integrity and cortico-subcortical connectivity.

ChEIs: effetto sulla Aβ

Parenchymal Aβ deposits in the cortex, primarily consisting of diffuse as opposed to neuritic plaques, were 70% lower in DLB patients receiving cholinesterase treatment vs those who were untreated. This significant reduction in Aβ deposition was verified in a linear regression analysis.

Riv and perhaps also other ChE inhibitors are likely to interfere with disease pathology particularly as it relates to the genesis of plaques.

Galantamine dramatically reduced Aβ 1-40-induced cellular apoptosis in SH-SY5Y human neuroblastoma cells. Disease-modifying effects of the drug could be due to an additional effect on Aβ aggregation and/or toxicity.

► We found lower incidence rates of dementia in the 2000 subcohort than in the 1990 subcohort, albeit not significant.

► There are several possible explanations for our observation of a decreasing incidence of dementia: 1) the 2000 subcohort was higher educated; 2) the implementation of preventive treatments and reduction in vascular risk factors at the population level; 3) a decline in stroke incidence itself could also attribute to a decreasing incidence of dementia.

► Our study suggests that the dramatic rise in absolute numbers of people living with dementia in the coming years may be slightly less enormous than has previously been reported.

Quale futuro?

Stopping Alzheimer’s Before It Starts

Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms.

Quale futuro?
In conclusione

- Usare al meglio i farmaci che già abbiamo
  - Partire il più presto possibile (stadi preclinici?)
  - Periodi molto lunghi
  - Ottimizzare i dosaggi terapeutici
  - Ottimizzare le strategie terapeutiche (switch)

«Persino allora, più di un anno prima, nella sua testa, non lontano dagli orecchi, dei neuroni venivano strangolati a morte, troppo in silenzio perché lei li sentisse. Si potrebbe insinuare che le cose andavano così insidiosamente male che erano stati i neuroni stessi a dare il via a una serie di eventi destinati a condurlì alla distruzione. Che fosse omicidio molecolare o suicidio cellulare, non erano in grado di avvertirla di quello che stava succedendo, prima di morire».

Genova L. Perdersi. Milano: Piemme; 2010
Gli inibitori delle colinesterasi possono avere un effetto disease-modifying?