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Comparative efficacy of selegiline versus rasagiline in the treatment of early Parkinson's disease

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Abstract. – OBJECTIVES: The monoamine oxidase B inhibitors selegiline and rasagiline have not been compared in head-to-head clinical trials in patients with early Parkinson's disease. The aim of this review was to compare the efficacy of these two agents in this setting.

MATERIALS AND METHODS: Randomized, placebo-controlled trials with an endpoint of the mean change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) total score were included. Analysis included calculation of the standardized mean differences (SMDs) with 95% confidence intervals (CIs) and Forest Plot analyses for comparisons of pooled results.

RESULTS: Five studies with selegiline (*n* = 1029) and four with rasagiline (*n* = 820) were included. Treatment duration was 2.5-9 months. Both selegiline and rasagiline showed significant SMDs versus placebo (–0.690, 95% CI –0.811, –0.569 and –1.025, 95% CI –1.230, –0.820; respectively), indicating a significant effect of both drugs on UPDRS. The SMD between selegiline and rasagiline was not significantly different (SMD 0.079; 95% CI –0.010, +0.167).

CONCLUSIONS: It appears that selegiline and rasagiline have comparable efficacy in improving Parkinsonian symptoms in patients with early stage disease.

Key Words:
Parkinson's disease, Rasagiline, Selegiline.

Introduction

Drug treatment of Parkinson's disease is still suboptimal, and new data are required to better inform therapeutic decisions in the treatment of this disorder[1]. Among the marketed antiparkinsonian agents, monoamine oxidase B (MAO-B) inhibitors are extensively used for symptomatic treatment because they increase synaptic dopamine (DA) levels by inhibiting DA catabolism[2]. Two MAO-B inhibitors, selegiline and rasagiline, are licensed in Europe and North America for the symptomatic treatment of early Parkinson's disease; in addition, they are used to reduce off-time in L-3,4-dihydroxyphenylalanine (L-DOPA)-treated patients with motor fluctuations[2].

The efficacy of both agents is supported by a robust bulk of evidence[3,4]. However, selegiline and rasagiline have never been directly compared in head-to-head trials. A meta-analysis published by Stove et al[5] in 2011 suggested that selegiline and rasagiline have comparable efficacy in the treatment of Parkinson's disease. However, this meta-analysis also included other antiparkinsonian agents and did not specifically focus on a direct comparison between selegiline and rasagiline.

The aim of the current review was a direct comparison of the efficacy of selegiline and rasagiline in the treatment of early Parkinson's disease.

Materials and Methods

Sources of Information

Twenty-one articles on either selegiline or rasagiline in the treatment of early Parkinson's disease were retrieved by a literature search of bibliographic databases using relevant keywords. Of these, three were observational studies, while 18 were randomized, placebo-controlled trials and were, therefore, further considered for inclusion in this analysis. Nine of these studies were included in the review because their main endpoint was the change from baseline in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS) 2.5-9 months after treatment initiation (Table I). Selegiline was used in five studies (*n* = 1029), and rasagiline in four studies (*n* = 820).

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Table I. Characteristics of trials included in the review.

Trial	Study treatment	No of patients (active treatment/ control)	Total follow-up	Follow-up considered in the meta-analysis (months)
Olanow et al 1995[9]	Selegiline + bromocriptine vs placebo + bromocriptine	22/19	14 months	3
	Selegiline + carbidopa/levodopa vs placebo + carbidopa/levodopa	20/21	14 months	3
Shults 1993[10]	Selegiline vs placebo	194/198	24 months	3
(DATATOP)	Selegiline + tocopherol vs placebo + tocopherol	106/76	24 months	3
Larsen et al 1999[11]	Selegiline + levodopa vs placebo + levodopa	66/76	5 years	3
Pålhagen et al 1998[12], 2006[a]	Selegiline vs placebo	81/76	7 years	3
Allain et al 1993[13]	Selegiline vs placebo	43/31	3 months	3
Rabey et al 2000[14]	Rasagiline vs placebo	13/18	12 weeks	3
Parkinson Study) Group 2002[15], 2004[a] (TEMPO)	Rasagiline vs placebo	134/138	12 months	6
Stern et al 2004[16]	Rasagiline vs placebo	15/13	10 weeks	2.5
Olanow et al 2009[17] (ADAGIO)	Rasagiline vs placebo	238/251	18 months	9

[a]Data from two publications, the 2004 publication of the TEMPO trial and the Pålhagen (2006) publication, were not included in the review because they were the final analyses of studies that had been published previously (TEMPO 2002 and Pålhagen 1998, respectively); the Pålhagen 1998 and TEMPO 2002 publications were included in the review.

Statistical Methods

Firstly, the difference between active treatment (selegiline or rasagiline with or without L-DOPA) and placebo in the change from baseline in total UPDRS score was calculated. Other concomitant treatments administered as study drug (ie, in a randomized fashion) were considered as strata, and analyses were stratified accordingly.

In order to compare studies with different sample sizes, we calculated standardized mean differences (SMD) and the related 95% confidence intervals (CI). Results for each drug were pooled by applying a statistical weight to take into account the different sample sizes of the studies (Forest Plot analysis). The same procedure was used to calculate the standardized difference between the pooled samples of selegiline and rasagiline.

Results

Figure 1 shows the results of the Forest Plot analysis. The treatment effect was significantly higher than the placebo effect in 7 out of 9 studies. In two studies with rasagiline, the Rabey study and the TEMPO study, the treatment effect was lower than the placebo effect.

The pooled estimate for the effect of selegiline showed a SMD of −0.690 (95% CI: from −0.811 to −0.569), thus demonstrating a statistically significant advantage of selegiline over placebo.

Similarly, the pooled estimate for the effect of rasagiline showed a SMD of −1.025 (95% CI: from −1.230 to −0.820), indicating a statistically significant advantage of rasagiline over placebo.

The overall difference between selegiline and rasagiline did not reach statistical significance (SMD for selegiline vs rasagiline: 0.079; 95% CI: from −0.010 to 0.167), indicating that selegiline and rasagiline had comparable efficacy on the primary endpoint in the analyzed studies.

Discussion

Overall, the results of our review indicated a similar efficacy of selegiline and rasagiline in reducing the total UPDRS score from baseline up to 9 months after treatment initiation. Both drugs were more effective than placebo. This is in contrast to a recent indirect meta-analysis by Jost et al. which reported a statistically significant advantage for rasagiline over selegiline in UPDRS total score[6].

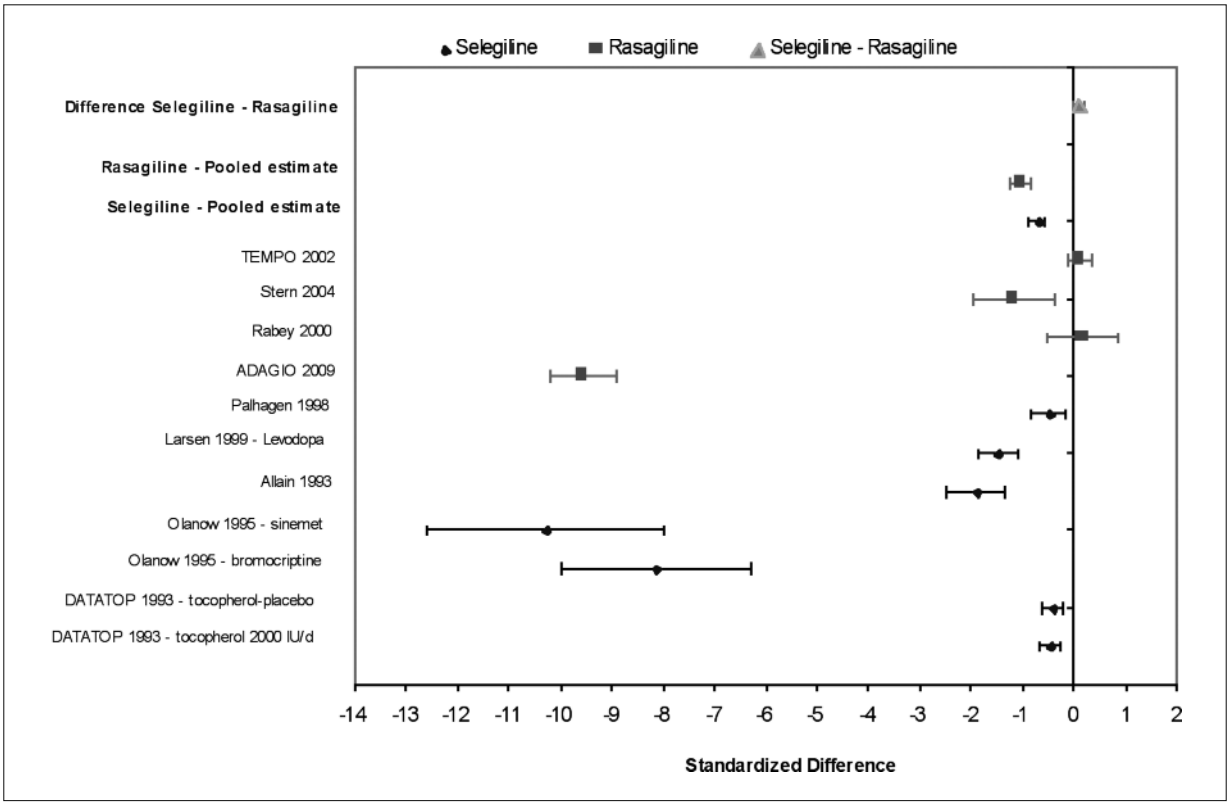

Figure 1. Forest plot of standardized mean differences for active treatment versus placebo, or selegiline versus rasagiline.

We decided to select studies using the change in total UPDRS score from baseline to month 2.5–9 of drug treatment as a primary endpoint. UPDRS is the most commonly used scale in clinical studies of Parkinson's disease; it encompasses assessment of all motor symptoms, and examines the whole clinical spectrum of symptoms of Parkinson's disease[7]. However, the use of a single endpoint, although robust and tightly related to clinical practice, limits the power of the present analysis. In addition, we only selected clinical studies with patients affected by early Parkinson's disease. These patients represent the main target population for treatment with selegiline or rasagiline because early Parkinson's disease is more susceptible to the potential neuroprotective activity of selegiline and rasagiline, and the disorder may progress faster in these patients[8]. We cannot rule out that different results may have been obtained if other endpoints or other study populations were considered.

The comparable efficacy of selegiline and rasagiline reported in the present report is in line with the results of the meta-analysis by Stowe et al[5], although the latter did not focus on a direct comparison between these drugs. Taken together, these two publications support the recent view by Fabbrini et al[4] that it is time for a "reappraisal" of the role of selegiline in the treatment of Parkinson's disease. In addition to the results of study presented here showing symptom improvement with selegiline, clinical experience with selegiline suggests that this drug reduces the progression of Parkinson's disease, and delays and reduces the requirement for L-DOPA[4].

Conclusions

Both selegiline and rasagiline might be considered equally effective in early stages of Parkinson's disease.

Statement of Interests

Stefano Marconi is an employee of Chiesi Farmaceutici S.p.A. Thomas Zwingers is an employee of CROS DE GmbH, a CROS NT Group company, who provided statistical analysis sponsored by Chiesi Farmaceutici S.p.A. We thank Tracy Harrison of inScience Communications,

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