Basal Ganglia 2 (2012) S17–S26

Contents lists available at SciVerse ScienceDirect

Basal Ganglia

journal homepage: www.elsevier.com/locate/baga

Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease

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ARTICLE INFO

Article history:
Available online 15 June 2012

Keywords:
Rasagiline
Selegiline
Parkinson's disease
Meta-analysis

ABSTRACT

Introduction: Selegiline and rasagiline are established in the treatment of Parkinson's disease. As no direct comparative randomised controlled trials on these drugs are available, an indirect meta-analysis was conducted.
Objective: Goal of the meta-analysis was to examine the clinical differentiation between rasagiline and selegiline based on efficacy and safety in Parkinson's disease.
Methods: Literature databases, study registries and references of relevant publications were the basis of our literature search. Studies were selected according to Jadad and Delphi criteria. The analysis used a fixed effects model based on standardised mean differences for efficacy criteria and risk differences of safety outcomes. As outcomes, UPDRS (primary) and UPDRS motor functions, mental and ADL, the Schwab and England scale, the off-time as well as safety as secondary outcomes were used.
Results: Rasagiline showed a statistically significant advantage in the primary endpoint UPDRS total scores (monotherapy: $p = 0.048$, sensitivity analysis: $p = 0.023$; pooled analyses: $p = 0.043$, sensitivity analysis $p = 0.014$) and the secondary endpoint UPDRS motor functions (monotherapy: $p = 0.049$, sensitivity analysis $p = 0.031$; pooled analyses: not significant, sensitivity analysis: $p = 0.046$). For the other secondary outcome parameters, a numerical advantage for rasagiline was found. Discontinuation rates due to adverse effects showed a tendency in favour of rasagiline. Risk for adverse events such as dizziness, hallucinations, diarrhoea and syncope were lower with rasagiline than selegiline (each $p < 0.15$).
Conclusion: This meta-analysis showed a statistically significant and clinically relevant advantage for rasagiline over selegiline in the primary endpoint. The superiority of rasagiline was further substantiated with advantages in tolerability and safety.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases and mainly affects the elderly. Its prevalence in Germany is around 100–200 patients per 100,000 inhabitants and at approx. 1800 per 100,000 inhabitants in people aged 65 and older [1].

Idiopathic Parkinson's syndrome is characterised by degeneration of the dopaminergic neurons in the substantia nigra, resulting in dopamine deficiency. Nevertheless it is not just a loss of dopaminergic neurons in the substantia nigra, but rather a multisystem degeneration, which affects other neurons and the transmitter systems as well. This leads to the characteristic motor dysfunctions such as tremor, rigour and akinesia/bradykinesia. However, PD also displays non-motor symptoms such as autonomic and psychiatric symptoms, sleeping disorder and pain [2].

Symptomatic treatments e.g., levodopa, COMT inhibitors and monoamine oxidase type-B inhibitors (MAO-B inhibitors), have a direct or indirect dopaminergic effect. For early-stage PD, the guideline of the "Deutsche Gesellschaft für Neurologie" (German Society for Neurology [DGN]) recommends initial treatment with only one substance (monotherapy) and then a combination of preparations (combination therapy) if, as the disease progresses, the symptoms can no longer be sufficiently controlled. MAO-B inhibitors are recommended for monotherapy in the early stage and for the combination therapy with levodopa in the advanced stages of PD [1]. Two preparations of the MAO-B inhibitors class are currently available: selegiline and rasagiline.

Monoamine oxidases (MAO) are catabolic enzymes of which two isoforms are known: MAO-A, which mainly exists in the digestive tract, and MAO-B, which can be found mainly in the brain. Selegiline and rasagiline are selective irreversible MAO-B inhibitors and

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http://dx.doi.org/10.1016/j.baga.2012.05.006

thus inhibit the metabolism of dopamine, thereby elevating the levels of endogenous dopamine, but also of exogenously supplied dopamine through pharmacologic treatment.

Even though selegiline and rasagiline share this primary mechanism of action, there are significant differences between the two drugs. Selegiline was approved for the treatment of PD in the US in 1979. Selegiline is a propargylamine-derivative of L-amphetamine and is metabolised *in vivo* to its major toxic metabolites L-amphetamine and L-methamphetamine, both of which are known to cause adverse effects such as restlessness and sleeping disorders [3]. Rasagiline is a second-generation MAO-B inhibitor which was launched in 2005. Chemically, rasagiline is an indane derivative that does not generate any amphetamine metabolites; its main metabolite is aminoindane which displays dopaminergic and neuro-protective characteristics in vitro and *in vivo*. The binding specificity for MAO-B of selegiline and rasagiline is comparable. However, the potency of MAO-B inhibition by rasagiline is greater than by selegiline [4]. Neuro-protective effects were shown in vitro for both selegiline and rasagiline [4]. Both substances also demonstrated neuro-protective effects in animal studies; however, rasagiline additionally showed a regenerative effect on signs of degeneration in the substantia nigra [4]. Furthermore, in the case of rasagiline, there are clinical indications that it slows down the course of the disease using a delayed-start trial design which has been approved by the competent authorities [5]. Clinical data which demonstrate the disease-modifying effect of selegiline are missing. The neuro-protective effect is also seen in preclinical data where results of selegiline show that this effect is antagonised by the amphetamine metabolites of the drug [6]. In contrast, rasagiline and its metabolite aminoindane show a neuro-protective effect [6].

The purpose of this analysis was to compare the symptomatic efficacy and tolerability of selegiline versus rasagiline in both mono- and combination therapy, as no direct comparative clinical studies between selegiline and rasagiline are available. Thus, in the present analysis, existing data are compared via an indirect meta-analysis. Effects of both drugs were examined in randomised placebo-controlled studies, so that the placebo can be used as a common link for an indirect comparison.

The validity of such indirect comparisons was examined and discussed in detail [7–9]. They are well-established in the comparison of treatments when no or only few direct comparisons are available. The main criteria for performing a meta-analysis is the availability of published data on randomised controlled studies of high quality and the application of an adjusted procedure during the statistical analysis. The guideline of the Cochrane Collaboration, which was used as the basis for the present publication, is considered to be the standard method of meta-analyses, including indirect meta-analyses [10–12].

Methods

Search for relevant studies

A systematic search for randomised placebo-controlled studies on selegiline or rasagiline in PD was conducted according to the criteria of the Cochrane Collaboration [12], as it was used, for instance, by Macleod et al. (2005) [13] when compiling a Cochrane review on the administration of MAO-B inhibitors in early PD. The database search included all studies up to 2009. The following databases were used: CENTRAL (Cochrane Central Register of Controlled Trials), DIMDI (incl. Medline, Embase, Psyndex, Biosis, Sci Search, Derwent Drugfile, ISTPB, IPA) as well as manual searching (including supplements, congress proceedings, references of relevant reviews, overviews).

The keywords used at CENTRAL were "Parkinson's disease*", "selegiline*" and "rasagiline*". The ones used at DIMDI were "rasagiline*", "selegiline*", "human*", "randomised controlled study", "placebo control", "blind (mono, double)", "meta-analyses", "review", "overview". The terms used via manual searching were "rasagiline*", "selegiline*", "randomised", "control" and "placebo".

The search was intentionally extensive in order to identify all suitable studies. The result of this search was then extracted on the basis of inclusion and exclusion criteria. Further publications were identified by analysing study databases/registries (FDA and European Clinical Trials databases) and literature references of relevant publications.

Inclusion/exclusion criteria

As recommended by the Cochrane Collaboration [12], the searched, randomised controlled studies were examined as to possible bias due to the study design as well as the quality of the publication. The quality of the publication was evaluated by means of two methods: Jadad [14] and the Delphi method [14], [15]. See Table 1.

Regarding the study design, the following inclusion criteria were applied:

- randomised placebo-controlled studies,
- rasagiline 1 mg/day or selegiline as monotherapy or adjunct therapy in PD,
- outcome measures were based on clinically relevant scales (Unified Parkinson Disease Rating Scale (UPDRS)) [15–17], Columbia University Rating Scale (CURS) [18]) or Schwab and England scale [19],
- daily off-time and
- safety and tolerability documentation.

The following studies were excluded prior to analyses:

- cross-over studies,
- parallel studies with a treatment duration <10 weeks,
- discontinuation studies,
- studies without control groups with a placebo treatment or no treatment and
- long-term studies without clinically relevant efficacy data (treatment duration $\leqslant$12 months).

In these meta-analyses, the efficacy of selegiline and rasagiline was evaluated on the basis of the earliest control visit. This neutral criterion is applied, as subsequent control visits are irregularly performed. In these meta-analyses, the ITT analysis was used.

Statistical methods

Efficacy was assessed by standardised mean differences (SMD) of the outcomes from the included clinical studies. The primary outcome for the efficacy was the difference between post and pre-scores of the total UPDRS or its precursor CURS at the time of the first control examination. As secondary outcomes, the UPDRS sub-scales motor functions, ADL and mental were analysed as well as the Schwab and England scale and the daily off-time. The meta-analysis was conducted separately for the monotherapy and the adjunct therapy of early PD and, on the pooled data of all studies, for both monotherapy and adjunct therapy (here: pooled analyses).

Secondary outcome parameters were safety and tolerability i.e. the rate of study discontinuations during the entire duration in all included studies. The basis of this comparison was the risk difference for study discontinuations between active substance and