Azilect in Parkinson’s Disease

LEVDOPA has been the mainstay of treatment for patients with Parkinson’s disease (PD) for the past 30 years and is still often used as first line treatment. In the long-term, however, levodopa-sparing strategies, such as using dopamine agonists, COMT inhibitors and monoamine oxidase-B inhibitors (MAO-B inhibitors), are necessary because of levodopa motor complications. Within a few years of levodopa treatment, many patients experience ‘end of dose’ fluctuations, off-periods and drug-induced dyskinesia. These may respond to treatment with adjunct dopamine agonists or COMT inhibitors, but these are not always effective or tolerated so we continue to need new treatments for PD.

The availability of the second generation MAO-B inhibitor – rasagiline - offers clinicians a promising new treatment for idiopathic Parkinson’s disease. Rasagiline can be used both as monotherapy and as an adjunct to levodopa to alleviate motor fluctuations. It is more potent than selegiline and has the benefit of absence of amphetamine metabolites. Moreover, the extension of the TEMPO trial hints that the drug may offer a disease-modifying effect in addition to its conventional activity as a MAO-B inhibitor; however this does require further investigation.

This article reviews the pharmacodynamics of rasagiline, the evidence from clinical trials and comments on the place of this new treatment in clinical practice.

Goals of treatment

The current aims of treating Parkinson’s disease are to alleviate the motor symptoms and, if possible, slow progression of the disease whilst improving quality of life for the patient and their carers.

Despite the initial considerable benefit obtained by most PD patients, long-term levodopa does not solve all of the problems faced by PD patients. In the more advanced stages of the disease, it does not improve many disabling motor and non-motor parkinsonian features. Managing motor complications such as fluctuating treatment responses, dyskinesias and dystonias, becomes a key objective in advanced disease. Around 40-60% develop such motor fluctuations within just four to six years of levodopa therapy.1 These problems tend to be more noticeable in patients with young-onset PD than in those who develop the disease in later years.2

Goals of PD treatment:
• Improve mobility
• Maintain function and quality of life
• Have minimal side effects
• Manage levodopa associated fluctuations and dyskinesias so decreasing daily ‘off’ time

The most common presentation of motor fluctuations is the wearing-off effect. This can manifest as early morning akinesia or each levodopa dose having a noticeable period of efficacy which appears to fade before the next dose is due. Patients may also develop ‘delayed-on’, ‘on-off’ or ‘no-on’ fluctuations and peak-dose or biphasic dyskinesias.3

Monoamine oxidase-B inhibitors

Dopamine agonists ( pergolide, pramipexole, ropinirole, cabergoline) and COMT inhibitors (entacapone and tolcapone) have been combined with levodopa to help manage motor fluctuations. However, adjunct use of these drugs produces only partial improvement as PD progresses, leaving patients with clinically significant off-periods, while adding complexity to their treatment schedule. Inhibition of monoamine oxidase-B (MAO-B) activity provides an alternative option for the treatment of levodopa-associated motor fluctuations. A meta-analysis of all published trials (17 randomised trials involving 3,525 patients) concluded that MAO-B inhibitors reduce disability, the need for levodopa, and the incidence of motor fluctuations without substantial side effects or increased mortality: Rasagiline is a newly available, second generation treatment for Parkinson’s disease with potent, selective, irreversible monoamine oxidase-B inhibitor properties.

Rasagiline pharmacodynamics

Rasagiline (N-propargyl-1-R-aminoindan) is more potent than selegiline, the only other MAO-B inhibitor on the current UK market. A 1mg dose of rasagiline almost fully inhibits platelet MAO-B activity in humans. Rasagiline and its metabolite, aminoindan, show a linear, dose-proportional increase in maximum blood concentration (Cmax) and area under the concentration time curve (AUC). The time to reach the maximum concentration (Tmax) is between 0.5 and 0.7 hours.1

Unlike selegiline, rasagiline is not degraded to amphetamine-like metabolites which have been associated with side effects such as raised blood pressure or increases in heart rate.4 Preclinical studies confirmed that rasagiline does not induce the alterations in blood pressure or heart rate observed with selegiline.2

Rasagiline has been shown to protect neurons against hypoxic injury, oxidative stress, cerebral trauma and N-methyl-4-phenyl-1,2,3,6-tetrahydroprpyridine (MPTP) induced neurotoxicity in animal models. The major metabolite of rasagiline, aminoindan, also shows dose-dependent inhibition of apoptosis in cell culture models. It is also possible that rasagiline promotes better function of surviving dopaminergic neurons, improves the connectivity of these neurons, or acts through another unidentified mechanism.5 The combination of rasagiline’s MAO-B inhibitory activity and potential disease-modifying action raises the spectre of offering clinicians and patients a significant new treatment for Parkinson’s disease.

Clinical trials

The safety, tolerability and clinical efficacy of rasagiline as adjunctive therapy to levodopa was tested in a multicentre, double-blind, randomised, placebo-controlled, parallel group study conducted for 12 weeks in 70 patients with PD (mean age 57.4; 32 patients had fluctuating PD).1 A beneficial clinical effect was observed in fluctuating patients treated with 0.5mg, 1mg or 2mg once daily. This was expressed as a decrease in total Unified Parkinson’s Disease Rating Scale (UPDRS) (23.0% in the rasagiline groups versus 8.5% in the placebo group). The treatment effect was still evident six weeks after drug discontinuation and the authors reported that the incidence and type of adverse experiences reported by patients receiving rasagiline were indistinguishable from those reported by patients receiving placebo. Interestingly, 15% of patients taking rasagiline had abolition of their off-periods.

In a 10-week, randomised, placebo-controlled phase II study of rasagiline in patients with early, untreated PD, the treatment was well tolerated.7 There were no occurrences of hypertension, bradycardia or other cardiovascular adverse experiences.

The TEMPO study (TVP-1012) as Early Monotherapy for Parkinson’s disease Outpatients was a 26-week, randomised, double-blind, placebo-controlled study in Canadian and US centres.8 It assessed the safety and efficacy of 1mg and 2mg rasagiline once daily in patients with early PD not requiring dopaminergic therapy (1mg n=134; mean age 61.6 years; mean disease duration 0.92 years; 2mg n=132; mean age 60.4 years; mean disease duration 1.15 years) against placebo (n=138; mean age 60.5 years; mean disease duration 0.94 years). Eligible patients included those older than 35 years
who had the presence of at least two of the cardi-
inal signs of PD and whose disease severity was not
greater than Hoehn and Yahr stage III.

The primary pre-specified measure of efficacy
was the change in the total Unified Parkinson’s
Disease Rating Scale (UPDRS) score between
baseline and 26 weeks. The results showed that
monotherapy with both doses of rasagiline was
effective: the adjusted effect size for the total
UPDRS was -4.20 units comparing 1mg and
placebo (95% confidence interval, -5.66 to -2.73;
p=0.001). Of the 138 subjects in the placebo
group, 16.7% (n=23) reached the secondary end
point of requiring levodopa therapy compared with
11.2% (n=15) of the 134 subjects treated
with 1mg rasagiline. The latter group showed sig-
nificant improvements in Parkinson’s Disease
Quality of Life scale (PDQUALIF) compared with
the placebo group. The benefit occurred primari-
ly in the subscale measuring self-image/sexuality,
with borderline effects on the social role subscale.
Overall, adverse events were no more frequent in
the treated group compared to placebo. Rasagiline
was not associated with hallucinations, oedema
and somnolence, potentially dose-limiting side
effects that can emerge with other PD drugs.

The magnitude of the symptomatic benefit
observed in this trial is comparable to that for
selegiline over a comparable six-month period.
Although the symptomatic effect observed with
rasagiline monotherapy in this study is more
modest than the effects observed with
dopamine agonists as monotherapy for PD, the
difference between these effects is relatively
small. The reported incidence of adverse events
is higher with dopamine agonists than was
observed for rasagiline in the TEMPO trial. Rasagiline’s simple once daily dosage and no
tritation led to a high level of compliance:
91.8% of patients taking the 1mg dose took
95% of their scheduled doses, compared with
89.4% taking the 2mg and 92% taking placebo.

The PRESTO™ (Parkinson’s Rasagiline: Efficacy and Safety in the Treatment of ‘Off’) trial was a multicentre, randomised, placebo-
controlled, double-blind, parallel group study of
472 people with PD who experienced at least 2.5
hours off-time a day, despite receiving optimal
therapy with other drugs. Patients were ran-
domised to rasagiline 1mg or 0.5mg once daily or
placebo. They had a modified Hoehn and Yahr
stage of less than 5 in the ‘off’ state, 30 years or
older and experienced at least 2.5 hours in the
off-state daily, as confirmed by a three-day home
diary. The main outcome measures were change
from baseline in total daily off-time measured by
patients’ home diaries during 26 weeks of treat-
ment and percentage of patients completing 26
weeks of treatment. Off-time decreased by 1.85
hours (29%) in patients treated with 1.0mg
rasagiline once daily, 1.41 hours (23%) with
0.5mg rasagiline once daily and 0.91 hour (15%)
with placebo. Patients on rasagiline had an
improved daily on-time without troublesome
dyskinesias compared to placebo; 0.51 hours in
patients treated with 0.5mg rasagiline once daily,
0.78 hours with 1mg rasagiline once daily.

Pre-specified secondary endpoints also
improved during rasagiline treatment, including
scores on an investigator-related clinical global
impression scale and the UPDRS.

**CLINICAL PRACTICE**

Rasagiline is taken as a single, oral, daily dose with
no need for titration and is thus easier to use for
both patients and clinicians than most other adjunct
therapies. This, plus its favourable tolerability profile
should make it a useful addition to current treat-
ments available for Parkinson’s disease.

As monotherapy, rasagiline significantly improves
tremor and bradykinesia and overall motor
function in de novo patients. In addition, the
drug improves activities of daily living and is well
tolerated. Starting patients with Parkinson’s disease
with rasagiline is a rational management strategy,
given its efficacy, good tolerability profile and the
avoidance of titration regimes.

In adjunct therapy, rasagiline is an effective and sim-
ple treatment when used in combination with lev-
odopa. It is a well tolerated adjunct in younger and
older patients. Rasagiline effectively reduced the time
spent in the off state and increased useful on-time,
making it a favourable candidate for the adjunct
treatment of Parkinson’s disease.

The number of patients discontinuing for any
reason or because of an adverse event was not sig-
nificantly different between treatment groups
(p=0.85). High patient acceptability was demon-
strated by the high compliance rates in this trial:
95% of patients taking 90% of their scheduled
doses. Adverse events mainly involved the gas-
trointestinal system (weight loss, vomiting and
anorexia) and were significantly more common in
patients treated with either dosage of rasagiline
compared with placebo. These appeared to be
dose related.

The LAGO (Lasting effect in Adjunct therapy
With Rasagiline Given Once daily) trial was an 18-
week, double-blind, multicentre study in which
687 patients were randomly assigned to 1mg once
daily rasagiline (n=231), 200mg entacapone with
every levodopa dose (n=227) or placebo
(n=229).11 Over a quarter of patients were ≥ 70
years (26%, 26% and 31%, respectively). Eligible
patients had a modified Hoehn and Yahr stage
of less than 5 in the off-state. They had to have
received optimum levodopa therapy and been sta-
ble for at least 14 days before baseline and have
had motor fluctuations for at least 1 hour every
day in the off-state during waking hours, not
including early morning akinesia. The primary
outcome was change in total daily off-time.

Rasagiline and entacapone equivalently
reduced mean off-time by 1.18 (p=0.0001) and
1.2 hours, respectively (p<0.0001) compared to
placebo (0.4 hours). The daily on-time without
troublesome dyskinesia increased by 0.85 hours in
both arms, compared to 0.03 hours in patients
treated with placebo (p=0.0005).

Changes in UPDRS scores also significantly
improved for activities of daily living during off-
time (-1.71 and -1.38 versus placebo, p=0.0001
and p=0.0006, respectively) and motor function
during on-time (-2.94 and -2.73, versus placebo,
both p<0.0001) in the rasagiline and entacapone
arms, respectively. The trial also looked at the
effects of rasagiline, entacapone and placebo on
Postural Instability and Gait Disorder (PIGD)
and freezing. These symptoms are, generally,
poorly responsive to PD therapy. Rasagiline-treat-
ed patients experienced a significantly greater
improvement in PIGD and in the UPDRS sub-
score for freezing than placebo-treated patients
(p<0.05). In contrast patients treated with enta-
capone showed no significant improvement com-
pared to placebo though a trend was evident.
In an ancillary study rasagiline added to levodopa
also significantly improved freezing of gait (FOG)
compared to placebo.

A smaller proportion of patients withdrew from
the rasagiline (10%) arm than either the
tacapone (13%) or placebo (15%) arm; and though
these differences were not significant. Rasagiline
was as equally efficacious and as well tolerated
in patients above and below the age of 70 years
and also equally efficacious and well tolerated in
patients taking or not taking concomitant
dopamine agonists.12

An important feature for patients noted in
this trial was that rasagiline significantly
improved motor symptoms before first morn-
ing drug administration compared to placebo,
meaning that patients did not have to wait for
their drug to work before they could move first
thing in the morning. In the UK, Azilect is
currently available as a 1mg tablet for use as
monotherapy and adjunct therapy.13

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