Initiation of treatment in early PD (evidences based)

Treatment of early Parkinson's disease (PD) may be divided into neuroprotective therapies, symptomatic therapies and various non-standard pharmacologic or non-pharmacologic therapies. Practical guides to direct treatment depend on the patients' symptoms, the degree of functional impairment, the expected benefits and risks of available therapeutic agents. The treatment of PD needs to be individualized, since patients often present with a unique set of signs and symptoms, response to medications and a multitude of other non-socioeconomic factors.

In this communication, we shall present the different agents which have been used in PD subjects with level of evidence of efficacy in different research studies. Then, we shall put our recommendation at the end.

Neuroprotective Therapies of PD

Neuroprotective therapy in PD implies that it would delay decline of motor symptoms and preserve the quality of life. In practical sense, one has to judge the effect of neuroprotective therapy by clinical markers. Potential clinical surrogate markers include ratings of motor impairment, general disability, quality of life measures, delay for the initiation of symptomatic therapy and time to a specific event, motor fluctuations, or death.

Potential neuroprotective therapies include the following.

Vitamin E

Although one unblinded and nonrandomized study without independent assessment suggested a slower rate of progression in early PD patients treated with vitamin E (3200 IU/day) combined with vitamin C (3000 mg/day),[1] another randomized, blinded study with 800 patients treated with 2000 IU of vitamin E/day or placebo (with or without selegiline) and followed for 14 ± 6 months did not show any difference between the vitamin E and placebo groups in the average time to require levodopa (hazard ratio 0.91, 95% CI 0.74–1.12).[2]

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Coenzyme Q10

Several open and controlled pilot studies on the symptomatic effects of coenzyme Q10 (CoQ10) revealed inconsistent results. The study of the Parkinson Study Group investigating possible protective effects of CoQ10 in early PD demonstrated that high doses of CoQ10 slow the progressive deterioration of functions in PD measured by the total score on the Unified Parkinson's Disease Rating Scale (UPDRS), but neither improve motor functions nor postpone the initiation of levodopa treatment.[3] Due to the lack of a washout phase and the fast and predominant effects of CoQ10 on activities of daily living (ADL) scores, it is not yet fully clear whether these effects might be a consequence of functional or antidepressive effects rather than neuroprotective actions.[3-5]

Riluzole

A single Class I, randomized, double-blind, placebo-controlled, 6-month trial evaluated riluzole 50 mg BID compared to placebo with a primary outcome of change in UPDRS. This pilot and extension study showed that riluzole (100 mg/day) was well tolerated in patients with early PD. No evidence of symptomatic effect of riluzole was observed. Because of the exploratory nature of the design and small size of the study, it was not possible to determine whether riluzole affected the natural history of PD.[6]

MAO-B inhibitors

Selegiline

The Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study[7] examined the ability of selegiline to delay the need for levodopa therapy in 800 patients with early PD who were not taking any PD medication. After 1 year, 97 subjects (24%) receiving selegiline versus 176 subjects (44%) not receiving selegiline experienced disability significant enough to require levodopa therapy. In addition, patients in the selegiline group had significantly better motor function scores compared with those taking

placebo. Given the observed symptomatic effect of selegiline, however, conclusions could not be drawn regarding any disease-modifying effects of the drug. Dry mouth was the only adverse event that occurred more commonly with selegiline than with placebo.

Rasagiline

In early monotherapy for PD patients (TEMPO) study,[8] a 26-week study of rasagiline in early PD, patients were randomized to receive 1 mg rasagiline daily, 2 mg rasagiline daily, or placebo. Motor function significantly improved with both doses of rasagiline compared with placebo. After the first 6 months of the study, those receiving placebo were switched to rasagiline 2 mg daily and patients in the initial rasagiline groups (1 or 2 mg daily) remained on their initial rasagiline doses for an additional 6 months. Significantly better motor function scores were noted in those initially treated with rasagiline than in those who were treated with placebo followed by 6 months of rasagiline.[9]

Long-term follow-up of 306 of the 360 subjects who completed the initial 6-month study indicated that after up to 6.5 years, the group that initially received rasagiline continued to have significantly better motor function scores compared with the delayed-start group (16% difference between groups).[10] Results of a larger, 9-month delayed-start study that was designed to further investigate this finding showed that early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2 mg per day did not. Because the two doses were associated with different outcomes, the authors concluded that the study results must be interpreted with caution.[11]

Dopa Agonists

Pramipexole

A randomized controlled trial (RCT) of 301 patients with early PD assessed treatment effects of levodopa versus pramipexole. Fewer patients receiving initial treatment for PD with pramipexole developed dopaminergic motor complications than with levodopa therapy. Despite supplementation with open-label levodopa in both groups, the levodopa-treated group had a greater improvement in total UPDRS compared with the pramipexole group making it inconclusive to say that pramipexol has any neuroprotective effect in PD.[12] In a study of dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression, eighty-two patients with early PD who were recruited were randomly assigned to receive pramipexole, with levodopa placebo (n = 42), or carbidopa/levodopa, with pramipexole placebo (n = 40). Clinical severity of PD was assessed using the UPDRS 12 hours off anti-PD medications,[13] The primary outcome was change in UPDRS score and change in SPECT with 2-beta-carboxymethoxy-3beta(4-iodophenyl)tropane (beta-CIT) labeled with iodine 123. At 46 months, there was no difference in the change from baseline in the UPDRS scores between the two treatment groups. At 46 months, a reduction of beta-CIT uptake of 16 ± 13.3 (pramipexole) versus 25.5 ± 14.1 in levodopa-treated patients (P = 0.01) was seen. However, many of the patients on pramipexole had concomitant levodopa treatment. The lack of a clinical correlate, the absence of a placebo control and the potentially different regulatory effects of levodopa or dopamine agonists (DAs) on the imaging marker preclude conclusions on any disease-modifying effects of pramipexole on the progression of PD.

To find out long-term effect of initiating pramipexole versus levodopa in early PD, the policies of initial pramipexole and initial levodopa use followed by open-label levodopa use resulted in similar self-reported disability, 6 years after randomization. Persistent differences favoring initial pramipexole were seen in the rates of dopaminergic motor complications, with less severe somnolence favoring initial levodopa.[14] This study also ruled out any neuroprotective effect of pramipexole.

Ropinirole

A pilot study examined 45 subjects in a prospective cohort treated with up to 1200 mg of levodopa and ropinirole up to 24 mg/day, followed for 2 years, and evaluated with fluorodopa Positron Emission Tomography (PET), which revealed no difference between the two groups. Completion rate was 82%.[15]

REAL-PET was a parallel-group prospective levodopa-controlled 2-year RCT conducted to assess the effect of ropinirole in 186 untreated patients with early PD. The primary endpoint to measure disease progression was percent reduction in bilateral putaminal uptake of levodopa on fluorodopa PET.[16] One hundred and sixty-two patients eligible for analysis were treated with ropinirole (up to 24 mg/day) or levodopa (up to 1000 mg/day) for up to 24 months. Both the groups could also be supplemented with levodopa or with stable doses of amantadine or anticholinergics throughout the study. Completion rate was 63%. The reduction in the ropinirole group was 13.4% as compared to 20.3% in the levodopa group (P < 0.001), but the same limits as discussed for the pramipexole study preclude any firm conclusions on the effect of ropinirole on PD progression.

Other DAs

There are several DAs such as bromocryptine, pergolide, apomorphine, cabergoline, lisuride, piribedil, and rotigotine. Among these, bromocryptine and cabergoline are available in India. Both are ergot derivatives. Bromocryptine is the weakest clinically in relation to others. Cabergoline is costly. Choosing a DA depends on how much it can be tolerated by the patients and its efficacy. Adverse effects may be the deciding factor regarding a selection. Non-ergot compounds should be preferred to ergot derivatives because of fibrotic adverse reactions and the risk of restrictive heart valve changes.

Levodopa

A randomized, double-blind, placebo-controlled ELLDOPA trial[17] evaluated 361 patients with early PD who were assigned to receive carbidopa–levodopa at a daily dose of 37.5 and 150 mg, 75 and 300 mg, or 150 and 600 mg, respectively, or a matching placebo for a period of 40 weeks, and then to

undergo withdrawal of treatment for 2 weeks. The primary outcome was a change in UPDRS scores at baseline and at 42 weeks. Neuroimaging studies of 142 subjects were performed at baseline and at week 40 to assess striatal dopamine-transporter density with the use of ^{123}I β -CIT uptake [*imaging of the presynaptic dopamine transporters using (^{123}I) beta-CIT used as a diagnostic marker for nigro-striatal degeneration*]. Patients randomized to all levodopa doses had significantly better UPDRS scores than patients on placebo, with the greatest improvement seen on the highest dose. Change in UPDRS on placebo was 7.8 (SD ±9), at a dose of 150 mg levodopa was 1.9 (SD ±6), at 300 mg was 1.9 (SD ±6.9), and at 600 mg was −1.4 (SD ±7.7). These results suggest that patients on a higher dose of levodopa had sustained functional improvement compared to their baseline even after a 2-week washout. However, it is possible that this washout period was not sufficient to exclude a persistent symptomatic effect. Patients on the highest dose of levodopa did develop more dyskinesias, but it is unclear whether this reflects a dose effect or disease progression. There was no significant difference in beta-CIT uptake across the groups. In a *post-hoc* analysis that included only patients with abnormal baseline beta-CIT scans, patients on high dose levodopa had greater reduction on beta-CIT uptake. These results are inconsistent and do not allow one to conclude definitely on the impact of levodopa on PD progression.

Other neuroprotective therapies

Due to nonrandomized design and nonindependent outcome assessment, the potential role of thalamotomy[18] and amantadine[19] as neuroprotective agents is difficult to assess. There are certain trophic factors which promote survival of DA neurons, such as glial cell line–derived neurtotrophic factor (GDNF) and neuroimmunophilins. Inflammations mediated nerodegeneration by the production of cytokines and prostaglandins have been advocated in PD and role of minocycline as an anti-inflammatory agent has not been found effective. Certain agents have been used as apoptotic agents, but have not been successful in the experimental stage.

Symptomatic Therapies for PD

Amantadine

Rigorous analysis of the six randomized controlled trials of amantadine reveals insufficient evidence of its efficacy and safety in the treatment of idiopathic PD.[20] Amantadine is more helpful in managing dyskinesia associated with dopaminergic therapy.

Anticholinergics

As monotherapy or as an adjunct to other antiparkinsonian drugs, anticholinergics are more effective than placebo in improving motor function in PD. Neuropsychiatric and cognitive adverse events occur more frequently on anticholinergics than on placebo and are a more common reason for withdrawal than lack of efficacy. Results regarding a potentially better effect of the anticholinergic drug on tremor than on other outcome measures are conflicting and data do not strongly support a differential clinical effect on individual Parkinsonian features. Data are insufficient to allow comparisons in efficacy or tolerability between individual anticholinergic drugs.[21]

MAO-B inhibitors

Selegiline[22] and rasagiline[8] have both been compared with placebo in good quality RCTs and they were seen to improve parkinsonism better than placebo. They can therefore be considered efficacious.

Dopa agonist as monotherapy

A meta-analysis of RCTs of DA as monotherapy for the early treatment of PD showed superior efficacy but more frequent adverse events compared to placebo. However, the clinical benefit is often delayed and the potency is lower than L-dopa. The use of DA is an effective treatment option for the treatment of early PD.[23]

Levodopa

Standard levodopa has been tested in a placebo-controlled RCT, which confirmed its long-established antiparkinsonian efficacy in early PD.[17]

Apomorphine

It is being only used subcutaneously and has never been tested as monotherapy for the treatment of PD at this early stage.

COMT inhibitors

These drugs are only active when combined with levodopa and are therefore not efficacious as monotherapy in the treatment of untreated patients with early PD.

DAs versus levodopa

On up to 2 years of open extended follow-up of the CALM-PD subjects,[14] it was concluded that the policies of initial pramipexole and initial levodopa use followed by open-label levodopa use resulted in similar self-reported disability, 6 years after randomization. Persistent differences favoring initial pramipexole were seen in the rates of dopaminergic motor complications, with less severe somnolence favoring initial levodopa.

Two recent meta-analyses[23,24] confirm that motor complications are reduced with DAs compared to levodopa, but also establish that other important side effects are increased and symptom control is poorer with agonists. Larger, long-term comparative trials assessing patient-rated quality of life are needed to assess more reliably the balance of benefits and risks of DAs compared to levodopa.

Controlled release levodopa versus levodopa

Despite the progressive nature of PD, both the immediate-release and sustained-release carbidopa/levodopa formulations maintained a similar level of control in PD after 5 years compared with baseline in a blinded randomized parallel study of 618 patients in 36 centers worldwide. Additionally, the low incidence of motor fluctuations or dyskinesia was not significantly different between the treatment groups and may be partly attributed to the relatively low doses of levodopa used throughout the 5-year study.[25]

Agonist Monotherapy versus Another Agonist

There is no convincing evidence of clinically relevant differences in the efficacy of the currently available DAs when used for the treatment of early PD.

Levodopa/Carbidopa/Entacapone versus Levodopa/Carbidopa

One recent multicenter, randomized, double-blind study[26] investigated whether treatment with levodopa/carbidopa/entacapone when compared with levodopa/carbidopa improves the quality of life in PD patients with no or minimal, nondisabling motor fluctuations. One hundred and eighty-four patients on three to four equal doses of 100/25 to 200/50 mg levodopa/carbidopa or levodopa/benserazide, 0–3 hours of nondisabling OFF time over a 48-hour period and no dyskinesia were randomized to levodopa/carbidopa/entacapone or levodopa/carbidopa treatment for 12 weeks. The primary outcome measure was quality of life as assessed by the PDQ-8. Secondary outcome measures were the UPDRS parts I–IV and the wearing off card. Treatment with levodopa/carbidopa/entacapone resulted in significantly greater improvements in PDQ-8 scores compared to treatment with levodopa/carbidopa (mean difference 1.4 points, $P = 0.021$). Statistically significant improvements were seen predominantly in nonmotor domains (depression, personal relationships, communication, stigma, all $P < 0.05$; dressing $P = 0.056$). Patients who were randomly assigned to levodopa/carbidopa/entacapone also showed significantly greater improvement in UPDRS part II scores ($P = 0.032$), with UPDRS part III scores showing borderline significance. Differences in UPDRS part I and IV and wearing off card scores were not significant. They concluded that treatment with levodopa/carbidopa/entacapone results in improved quality of life compared with levodopa/carbidopa in PD patients with mild or minimal, nondisabling motor fluctuations. But long-term studies are required to evaluate the potential long-term benefits of this treatment strategy.

Various Non-standard Pharmacologic or Non-pharmacologic Therapies of PD

Use of complementary medication and treatment is common in patients with PD; 40% of patients in the United States and 54% of patients in the United Kingdom use treatments such as herbs, vitamins, massage and acupuncture.[27,28]

Among these, food therapy,[29-34] vitamin therapy,[35-37] acupuncture therapy,[38] manual therapy,[39-41] exercise therapy[42,43] and speech therapy[44,45] have been tried in various trials.

For patients with PD, exercise therapy may be considered to improve the function (Level C), but this effect persists as long as the patient continues with exercise. For patients with PD complicated by dysarthria, speech therapy may be considered to improve speech volume (Level C).

Indian Guidelines for Treatment of Early PD

Based on the above evidences, Indian guidelines for treatment of early PD are as follows.

Until agents with proven neuroprotective or disease-modifying effects become available, the choice of initial treatment must be tailored to each patient's requirements. Several factors should be considered when determining whether to initiate treatment and which treatment option to use. These factors include functional disability, disease severity, age, employment status, lifestyle, cognitive and psychiatric status, handedness, predominantly affected side, the presence of comorbid conditions and economic status. Once the decision has been made to start symptomatic treatment, the best choice for each individual patient must be identified. Moreover, drugs available locally are also important.

However, in an ideal situation, an effective evidence-based guideline will be as follows:

1. At this point of time, there is no definite neuroprotective therapy available for PD.
2. Mild symptoms and signs without functional impairment should be observed till mild functional impairment starts appearing.
3. In a patient with mild functional impairment, it is preferable to initiate with an MAO-B inhibitor (Level 1 evidence).
4. If or when MAO-B inhibitor is insufficient or symptoms worsen, the subject should be switched to or add levodopa/carbidopa or non-ergot dopa agonist (pramipexol or ropinirole).

In a patient older than 65 years, who has cognitive or psychiatric issues, or significant comorbidities, initiation of a low dose of levodopa and carbidopa preparation which is to be slowly increased as clinically necessary is recommended with or without an MAO-B inhibitor.

In a patient younger than 65 years, the choice is a DA or anticholinergics or amantidine which could be initiated or added to an MAO-B inhibitor. Dose is to be escalated as required and tolerated. Then, L-dopa and carbidopa preparation should be added when agonist monotherapy becomes insufficient or is not tolerated (Level 1 evidence).

1. Use of anticholinergics and amantidine in early PD has however lower level of evidence.
2. Evidence is still required to recommend starting levodopa/carbidopa/entacapone instead of levodopa/carbidopa when indicated.

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