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Biotherapies in neurological diseases

Biotherapies for Parkinson disease

Biothérapies dans la maladie de Parkinson

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INFO ARTICLE

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ABSTRACT

The clinical use of biotherapies in Parkinson disease already has 30 years history. The transplantation of dopamine fetal cells in the striatum of advanced patients has proved to be relevant in some patients but randomized efficacy trials in the US have provided disappointing results. However, cell therapies might come back on stage with the use of stem cells in the future. Gene therapy is a more recent strategy relying on viral vectors able to transduce genes coding either for the enzymes that can increase neurotransmitters production or genes for trophic factors. Several approaches have been developed in PD and have been experimented in patients. Although, some of the studies have evidenced insufficient clinical benefit, other programs, such as those using dopamine replacement techniques are promising. We find fresh hope in this field that might be the future of PD treatment. It remains however that advanced PD might not be the ideal condition to properly benefit from biotherapies and there is a need of studies at earlier stages of the disease, a time where major change in the disease course might be expected.

Mots clés :
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RÉSUMÉ

Les premiers essais de biothérapie dans la maladie de Parkinson datent maintenant d'il y a 30 ans. Les greffes de cellules fœtales dans le striatum de patients à un stade avancé de la maladie ont montré qu'elles pouvaient améliorer certains patients. Néanmoins, les essais contrôlés réalisés aux États-Unis ont été décevants. La thérapie cellulaire pourrait toutefois revenir au premier plan avec l'émergence prochaine des cellules souches. La thérapie génique est plus récente et repose sur l'utilisation de vecteurs viraux capables de transmettre des gènes codant soit pour des enzymes permettant la fabrication de neurotransmetteurs, soit pour des facteurs trophiques. Plusieurs approches différentes ont déjà été expérimentées chez les parkinsoniens. Si certaines de ces stratégies ont apporté des bénéfices insuffisants, il semble que les techniques visant à faire produire de la dopamine

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soient prometteuses. Elles pourraient révolutionner le champ thérapeutique de la maladie. Il n'en demeure pas moins que les formes avancées de maladie de Parkinson ne sont peut-être pas le stade idéal pour bénéficier de ces biothérapies. Nous avons besoin d'essais à des stades plus précoces qui pourraient s'avérer en particulier bénéfiques sur l'évolution de la maladie.

Parkinson disease (PD) has been the main disease for which biotherapies, i.e., cell or gene therapy, have been experimented in the last 30 years. Although considering that PD is only related to dopamine (DA) cell loss in the substantia nigra is an oversimplification, it has allowed the development of different strategies to replace DA cells or DA production in the striatum of advanced patients. This review aims to draw a schematic view of the main results and drawbacks of these strategies when applied to PD patients.

1. Cell therapies

The idea of replacing DA neurons in PD has emerged in the 1970s. The rationale was to use DA-producing cells able to overcome the neurochemical deficiency in the striatum of patients with PD and to reduce motor fluctuations and dyskinesias observed at the late stage of the disease. This strategy has been extensively experimented in rodent models of PD until the demonstration of the survival of human cells obtained from the ventral mesencephalon of abortion fetuses and the recovery observed in rats following striatal implantation of these cells [1]. These pivotal results opened the road for a human safety trial. It is important to remember that these strategies were designed and experimented long before the emergence of deep-brain stimulation (DBS).

From 1988 to 2003, several trials have been performed most of them being open-labelled and two were blinded and randomized. It is important to add that there was a general agreement across the different teams involved in transplantation trials to use common evaluation methods relying both on clinical protocols (CAPIT and CAPSIT [2,3]) and imaging of dopamine production using positron emission tomography (PET) and ^{18}F-DOPA. Reviewing all these studies in detail is not in the scope of this paper, therefore, we selected the main results to illustrate the benefits and limits of cell therapy in PD.

First of all, the proof of concept has been validated. Indeed, it is possible to graft DA fetal cells in an ectopic location, i.e., the striatum, instead of the natural site, which is the substantia nigra, and to obtain both survival and function of the grafted DA cells. Survival has been evidenced by post-mortem observations occurring more than 10 years after transplantation, revealing nerve fibres growing from grafted cells into the host striatum. The function of the transplanted cells has been demonstrated by PET studies, showing both the increase of ^{18}F-DOPA uptake induced in the striatum by the grafted tissue [4,5], and that DA produced by grafted cells reaches the D_2 receptors of the host striatal neurons [6]. Moreover, the increase of DA production obtained with transplantation is able to improve the function of cortico-striatal loops implicated in motor behavior [7].

Clinically, grafts can be associated with sustained motor improvement in some but not all transplanted PD patients. Some patients still have a graft-benefit more than 15 years after tissue implantation. Although open-label trials might be biased by marked placebo effects [8,9], correlations observed between ^{18}F-DOPA uptake improvement and clinical changes, even in small cohorts [5] suggest that the clinical changes are likely to reflect the real pharmacological action of transplants. The marked variability of the clinical changes induced by the grafts have been attributed to discrepancies in grafting procedures, or immunosuppressive regimens or age of fetal donors, but this would not explain intra-centre variability observed in all open-labelled studies. However, it seems that the number of donors used for each transplantation plays a major role in the clinical result [10], probably because the majority of grafted neurons do not survive in the host striatum. Altogether, recent reviews agree on the fact that open-labelled studies besides heterogeneous results have not allowed the emergence of a validated procedure that could be applied in efficacy, randomized trials.

Nevertheless, two such trials have been funded by the NIH at the end of the 1990s. Their originality is the use of ''sham surgery'': the non-grafted patients (''placebo'' arm) are anaesthetized and have a similar surgical procedure except that no needle pass the dura and enters the brain. Patients randomized in the placebo arm can be grafted if they wish at the end of the trial. Sham surgery has raised many ethical issues in European countries but is likely to be the only strategy able to overcome the major placebo effect associated with surgical techniques in PD patients [11]. Both NIH-funded trials failed to demonstrate a clinical benefit of the grafts when looking to the primary endpoint. Post-hoc analysis of the Colorado study suggested that younger patients (aged less than 60) had a significant improvement (34% reduction of motor UPDRS) compared to complete failure in patients aged more than 60 [12]. Unfortunately, 5 of the 33 patients who ultimately were grafted (20 + 13 from placebo group, all aged less than 60 at study entry) developed severe dyskinesias that were still present after complete L-DOPA withdrawal.

The second randomized trial aimed to evidence a ''dosing effect'' for transplants by comparing sham surgery, to 1 vs. 4 fetal donors transplanted bilaterally in the post-commissural putamen [13]. The study failed to demonstrate motor improvement on UPDRS-motor scale 2 years after surgery in both active arms of the trial, despite the fact that ^{18}F-DOPA uptake increased in the putamen of transplanted patients. It seems however that some of the patients selected for this trial did not have a satisfying levodopa response before surgery. It