Clinical Pharmacology

Disease Progress and Drug Action

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Outline

1. What is disease progress?
   ➢ Progress (status) and Process (mechanism)

2. Symptomatic or disease modifying?
   ➢ Can Regulatory Agencies help decide?

3. Disease modification
   ➢ Rheumatoid Arthritis, Multiple Sclerosis, COPD ?
   ➢ Parkinson’s Disease – confirmed benefit of levodopa

What is Clinical Pharmacology?

Clinical Pharmacology = Disease Progress + Drug Action

Clinical pharmacology can be described as the science of understanding disease progress (clinical) and drug action (pharmacology). Disease progress implies that the disease changes with time. Drug action refers to the time course of drug effect and includes pharmacokinetics, pharmacodynamics and a link model to account for delays in effect in relation to drug concentration. Clinical pharmacology is not a static description of the use of a drug but includes the time course of disease, drug concentration and drug effect.
Disease Progress Model

- Quantitative model that accounts for the time course of disease status, \( S(t) \):

  » “biomarkers”
  - Signs - physiological or biological measurements of disease activity

  » “clinical outcome”
  - Symptoms - measure of how a patient feels or functions
  - Survival - Dead or alive (or had a stroke or not, etc.)

A symbol to describe disease progress is ‘\( S \)’ i.e. the disease status. Disease status is expected to vary with time, \( S(t) \). Disease status may be defined in terms of clinical outcomes such as survival and symptoms or in terms of a biomarker. Biomarkers are also known as clinical signs when used by clinicians as diagnostic or prognostic variables.

Bone Mass in Humans

The time course of changes in bone mass (“knockenmasse”) with age (“alter”) is shown in men (blue line) and women (red line). The source (“quelle”) is cited as Dr A Walker from the University of Reading.
The link between low bone mineral density (biomarker) and the risk of bone fracture (outcome) is well known. This Swiss muesli was marketed with the claim that calcium and magnesium strengthen bone mass. Calcium and magnesium were added to the muesli in order to broaden its appeal to women concerned about developing osteoporosis.

The simplest model to describe changing disease status with time is linear. In general if the change is relatively small in relation to the time scale of observation then any disease progress curve will reasonably described by a linear function.

With any disease progress model it is possible to imagine a drug action that is equivalent to a change in the baseline parameter of the model. This kind of effect on disease produces a temporary offset. When treatment is stopped the response to the drug washes out and the status returns to the baseline. In many cases it is reasonable to suppose that the processes governing a delay in onset of drug effect will also affect the loss of effect but the offset effects of levodopa treatment in Parkinson’s disease are one exception to this assumption.
The action of cholinesterase inhibitors in Alzheimer’s disease is very similar for all drugs in this class. There is a delayed onset of benefit taking 2 to 3 months to reach its peak followed by continued progression of the disease at the same rate as expected from natural history progression. This is clear example of an offset type of drug action. If there is a disease modifying effect it is small and hard to detect without withdrawal of treatment.

Drug effects on the slope of a linear model lead to permanent changes in the disease status which are not reversed when treatment is stopped. The persistent change after stopping treatment is the hallmark of a disease modifying action if the natural history is linear.

A trial was undertaken in China in patients with moderate renal functional impairment. After 2 years of follow up they were randomized to treatment with a lead chelating agent. Patients who received chelation treatment had a rapid improvement in function which could be described by an offset effect. There was also a marked slowing of the rate of decline of renal function. This could be described by a slope effect but without washout of treatment it is not possible to distinguish a true disease modifying effect from a slow onset offset effect.
Disease Progress and Process Models

- Progress model describes the time course of disease status, $S(t)$

- Process model proposes an underlying mechanism to describe $S(t)$

\[
\frac{dS}{dt} = R_{form} \exp(-kt) - R_{loss} \exp(+kt)
\]


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Disease Modifying - Can FDA Help Decide?

- Rheumatoid Arthritis
  - Guidance for Rheumatoid Arthritis (2013)
  - No mention of disease modifying


- Webinar describing the guidance shows all drugs for RA as DMARDs (disease modifying anti rheumatic drugs) (2013)
- No definition of DMARD


DMARD=Disease Modifying Anti-Rheumatic Drug

FDA describes drugs used to treat rheumatoid arthritis as DMARDs but does not define what disease modifying means in public documents.

- Multiple Sclerosis
  - Multiple Sclerosis Outcome Assessments Consortium Data Acquisition Highlights (2012)
  - No mention of disease modifying


- “…all previous Phase 3 studies of disease modifying therapies (DMTs) in MS have included the effect on relapse rate as an efficacy endpoint.” (2013)
- No definition of DMT


DMT=Disease Modifying Treatment

FDA describes drugs used to treat multiple sclerosis as DMTs but does not define what disease modifying means in public documents.
Disease Modifying - Can EMA Help Decide?

- Multiple Sclerosis
  - Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis
  - Mentions disease modifying therapies
  - No definition of disease modifying


EMA has a Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. Mentions disease modifying treatments but no definition of disease modifying.

Chronic Obstructive Pulmonary Disease


The FEV1 is a measure of airway resistance. Tiotropium is an inhaled anticholinergic bronchodilator. FEV1 was measured before and after bronchodilatation with inhaled salbutamol (albuterol). Patients with chronic obstructive pulmonary disease (COPD) treated with placebo or with tiotropium show an initial symptomatic response which appears to be maintained in the tiotropium treated group. There is no indication of a disease modifying effect. Before bronchodilation, the annual rates of decline were the same in the tiotropium group and the placebo group: 30±1 ml per year. After bronchodilation, the annual rate of decline was 40±1 ml per year in the tiotropium group, as compared with 42±1 ml per year in the placebo group. Results of this kind of trial looking for disease modifying effects are still controversial because of naïve data analysis approaches that cannot distinguish symptomatic from disease modifying effects.

Niewoehner DE. TORCH and UPLIFT: what has been learned from the COPD "mega-trials"? COPD. 2009;6(1):1-3.
The DATATOP study was performed over a 2-year period but patients enrolled in the study were subsequently followed up for 8 years. The time course of disease status in Parkinson's disease and the effects of treatment were described by a disease progression model with symptomatic and disease-modifying effects of levodopa and deprenyl (selegeline). The NM-TRAN code for this analysis can be found in Holford et al. 2006.


Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.

The first patient in the DATATOP cohort shows the patterns that were eventually used to build a disease progress and drug action model. The initial rate of progression seems to be slowed when treatment with levodopa and deprenyl is used. In addition, there is a marked symptomatic effect which is primarily attributable to levodopa. It is not obvious what disease progression model is most suitable but it could be linear. Testing different model led to the conclusion that the disease progress approached an asymptote using a Gompertz model.
The effects of levodopa and deprenyl are shown. Both have offset effects and protective effects which was described by an action on the time constant of a Gompertz asymptotic model. See Holford et al 2006 for details of the model code.


The ELLDOPA study was based on the hypothesis that levodopa had toxic effects on dopaminergic neurones. If this hypothesis was true then it would suggest later treatment with levodopa would be preferable to earlier treatment.

The Parkinson Study Group which performed the DATATOP study was interested in asking if levodopa changes the rate of progression of Parkinson’s disease. They designed a trial that was simple in principle but it rested on a key assumption that symptomatic effects of levodopa would wash out within 2 weeks of stopping treatment. An analysis of patients in the DATATOP cohort who stopped levodopa showed treatment effects took much longer than 2 weeks to wash out (Hauser & Holford 2002).

When treatment was stopped after 9 months there was a loss of UPDRS response over the next 2 weeks but it did not approach the response seen in a parallel placebo treated group. The marked difference from placebo could be due to a true disease modifying effect or a very slow loss of symptomatic effect. The DATATOP model based analysis predicted that the difference from placebo was due to a combination of symptomatic and disease modifying effects.
The ELLDOPA study was simulated using the parameter estimates for disease progress and levodopa effects obtained from the ELLDOPA data (Estimated ELLDOPA). A similar simulation was performed using parameters predicted from the DATATOP cohort (Predicted DATATOP) and the levodopa washout study (Hauser & Holford 2002). The predicted difference from placebo in the three levodopa dose groups was very similar to the observed response. This is a form of external validation of the DATATOP model. It is a very strong test of the value of the model developed from DATATOP because it predicted the outcome of a trial with a very different design. The model based analysis of the ELLDOPA data used the same model as DATATOP and confirmed similar symptomatic and disease modifying effects.

The LEAP trial (Verschuur et al. 2019) randomized Parkinson's patients to inactive (“placebo”) or levodopa treatment for 40 weeks. At 40 weeks, patients still taking “placebo” were started on levodopa. 41% of patients in the “placebo” group were started on levodopa before 40 weeks for symptomatic reasons. The rate of UPDRS progression between 4 and 40 weeks was 50% slower in the early compared to the delayed start groups but not significantly different. The rate of UPDRS progression was reported as being faster in the delayed start group between 44 and 80 weeks which is not consistent with the figure (A) showing the time course.


Espay (2019) concludes there is no support for disease modifying benefits of levodopa but does not seem to be aware of the results of the DATATOP and ELLDOPA analyses which predict and confirm a disease modifying effect of levodopa (Holford et al. 2006, Chan et al. 2007, Ploeger & Holford 2011). Zarin et al. (2019) caution about the harm arising from uninformative clinical trials which may be uninformative because of inappropriate analysis. The LEAP trial (Verschuur et al. 2019) is uninformative because the intention to treat analysis wrongly assumes that all patients receiving inactive (“placebo”) treatment in the first 40 weeks. In fact 41% of patients were switched to levodopa because of unacceptable progression of symptoms. This means these patients would have slower progression in the first 40 weeks and any disease modifying effects from levodopa would be carried forward to the second 40-80 week period. This necessarily reduces the difference between the delayed and early start groups when evaluated at 80 weeks.

Ploeger B, Holford NHG. Confirmation of symptomatic and disease modifying effects of levodopa using the ELLDOPA study. [www.page-meeting.org/?abstract=2145]. PAGE.
**Conclusions**

- Disease progression captures changes in disease status with time
- Looking at graphs of disease time course can help understand natural history and effects of treatment
- Model based description can distinguish symptomatic from disease modifying effects of treatment
- Disease progression can help understand and predict disease outcome events
- Avoid intention to treat analysis for scientific investigation