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Repositioning 'old' drugs to treat rare diseases: arguing from the mechanism of action

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It is often hard to decide whether there are appropriate therapeutic options for patients suffering from rare diseases, in general. Randomised evidence based studies are lacking. In this situation, the use of existing drugs for new indications, i.e. repositioning, may be an attractive option, as the initial drug development research, which usually takes some years, has already been done (Figure 1). Moreover, the benefit-risk balance regarding appropriate dosages is already known in other disease that saves time as well. The new use can be immediately tested in nonclinical pharmacodynamic studies and clinical trials. This is already happening: in recent years, about 30% of the new drugs and vaccines approved by the US Federal Drug Administration concerned new indications for existing drugs (1).

Research into repositioning has yielded methods for identifying new options and new indications for existing drugs (2,3). Such studies can only be successful if the pathophysiological mechanisms that play a part in a particular disorder are known (3). Once these are known, the knowledge gained from research into other, less rare disorders with a similar pathophysiological mechanism can be used to select a drug. This is what is known as an 'orphan therapeutic indication' (using a common drug for a rare indication).

Some examples of new uses of 'old' drugs are listed in the table, but such repositioning is still highly uncommon for rare diseases, partly because health insurers are usually not prepared to reimburse the costs.

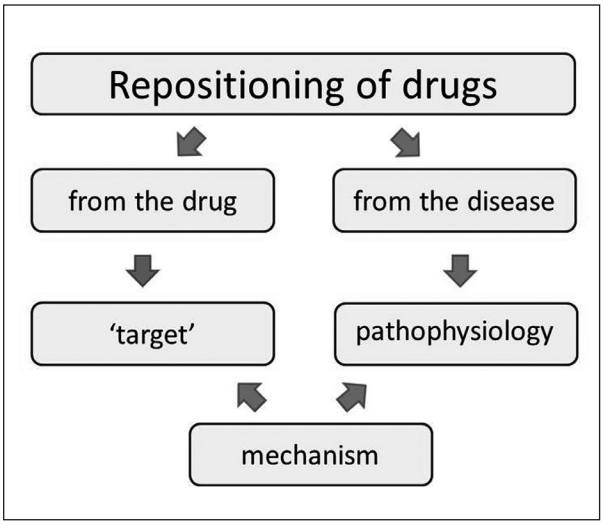

Fig. 1. Repositioning of drugs

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Case study: histiocytosis-X

We would like to argue for a different type of drug evaluation where rare diseases are concerned, illustrating our arguments with a few examples. The first example concerns the case of a 45-year-old woman who presented to her family doctor with severe dyspnea, and was referred to a pulmonologist. She was found to have extensive diffuse nodular interstitial lesions on the high resolution computer tomography CT (HRCT) scan, presenting a major diffusion problem (Figure 2a). A biopsy from the lung showed that she was suffering from the very rare disorder histiocytosis-X, which is associated with smoking (4,5). Giving up smoking is one major approach, which generally greatly improves the clinical condition. There are, however, patients for whom this does not work, and this woman was one of them. In some cases, the only solution may be a lung transplant. This treatment is, however, available to few patients, partly due to the shortage of donor organs. She was referred to the ild care team with the request to provide tailored therapeutic advice.

Pathophysiology

An important factor in the pathophysiological mechanism of histiocytosis-X is oxidative stress (5). Oxidative stress and anti-TNF-alpha also play a major part in COPD, which is also usually caused, or at least exacerbated, by smoking. Recent research has proved the value of roflumilast – a phosphodiesterase-4 inhibitor (PDE4 inhibitor) – in the treatment of COPD (6,7). The enzyme PDE4 is present in human inflammatory cells, particularly macrophages, eosinophils and neutrophils, which are important in the pathogenesis of COPD. These same cells are also involved in the pathogenesis of histiocytosis-X (3). Arguing from this similarity of mechanism, we initiated oral administration of roflumilast 500 µg daily.

After two months, the patient showed clear clinical improvement: she was less troubled by dyspnea and coughing, and the CT image was also much better. Despite the low cost of the therapy (about 50 euros a month) she was unfortunately unable to pay for this herself, and was forced to abandon the therapy. We only found out about this at her next checkup, about two months later. At that time, her condition had considerably deteriorated again. Since we considered this situation to be unethical, we decided to apply for reimbursement by the health insurer, and to supply her with the drug in the meantime. Based on our arguments and the data from the literature, the insurer decided to reimburse the drug for this patient. At the time of writing, she is continuing to improve: she feels clinically better, her pulmonary function has improved, as has the HRCT image (Figure 1b), where lesions have largely resolved.

Repositioning for a larger population

Another successful example of repositioning is thalidomide, which, combined with melphalan and prednisolone, is now licensed as a first-line therapy

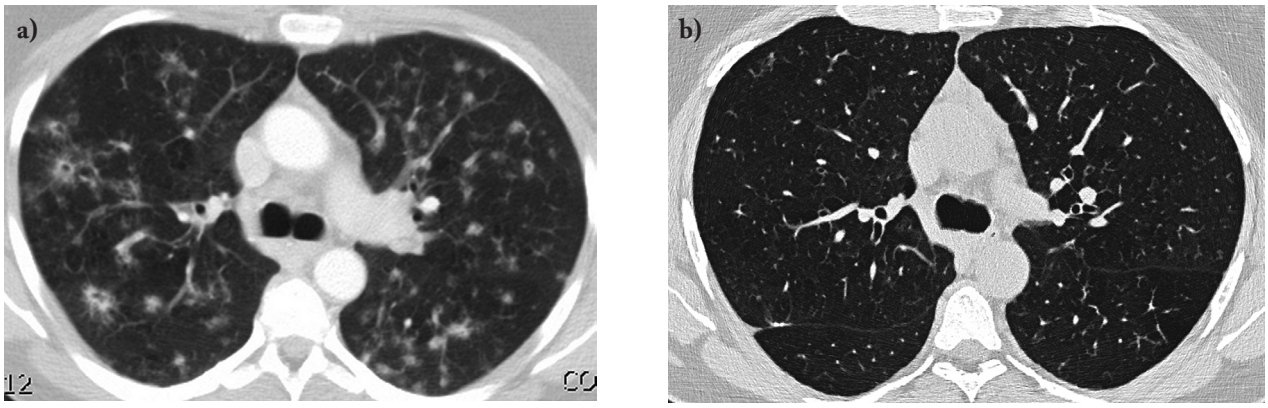

Fig. 2. HRCT before treatment (a), showing the characteristic combination of poorly defined nodules and cysts of varying sizes. HRCT after one year treatment with roflumilast: almost all lesions have disappeared (b)

for patients aged 65 years and older with multiple myeloma (also known as Kahler disease) (8). The drug is now also used for some refractory skin manifestations of sarcoidosis (see also Table 1).

But repositioning old drugs can also be beneficial to a much larger patient population, as is shown by the example of acetylsalicylic acid. This agent was marketed by Bayer in 1899 under the brand name Aspirin, initially to treat pain and fever. After 1960, the drug appeared to lose its popularity, due to side-effects such as gastric haemorrhage and kidney problems, and was largely replaced by paracetamol, which had fewer disadvantages and was also cheaper. By 1988, however, low-dose acetyl salicylic acid had been convincingly shown to prevent recurrent heart attacks, and the drug started an impressive come-back (9). By 2011, in the Netherlands alone, 1.3 million patients were using acetyl salicylic acid as antithrombotic agent. All in all, this is a highly successful example of drug rediscovery.

More recently, it was reported that the prodrug lansoprazole represents an excellent example of a valuable hit compound in an existing library that was missed by conventional drug screens (10). Using an innovative screen, a new activity was found for an old drug that supports the notion that novel screening platforms may uncover new antibiotics in old libraries. Better antibiotics capable of killing multi-drug-resistant Mycobacterium tuberculosis are urgently needed. Despite extensive drug discovery efforts, only a few promising candidates are on the horizon and alternative screening protocols are required. It was shown that the blockbuster drug lansoprazole (Prevacid), a gastric proton-pump inhibitor, has intracellular activity against M. tuberculosis. These findings provide proof of concept for hit expansion by metabolic activation, a powerful tool for antibiotic screens (10).

Repositioning old drugs requires not only research evidence, but also expert opinion based on the underlying pathophysiological mechanisms. Insurers should be willing to reimburse the use by patients with rare diseases of drugs that have not been specifically tested as a therapy for their disease, but which can be expected to be effective on the basis of pathophysiological similarities. PDE4 inhibitors have been successfully used to treat a number of other disease entities besides COPD, based on the pathophysiological mechanism involved, rather than on randomised studies (6,7). Negotiations with health insurers should result in clear agreements on criteria for reimbursement, for instance that the use of the drug should be based on the opinion of predesignated experts and evaluation of the effect in individual patients.

After a drug has been licensed, it can be marketed, thus entering a new phase in its development, in which prescribing doctors explore the product's possibilities as they go along. This may involve the drug being prescribed in case registered drugs are lacking,

Table 1. Some examples of drugs developed for a certain indication with new uses (8,9,11-20)

Drug	First indication	Mechanism of action	New use
acetylsalicylic acid	pain control	prostaglandin synthesis inhibition	inhibiting platelet aggregation
apremilast	treatment psoriatic arthritis	a phosphodiesterase-4 inhibitor (PDE4 inhibitor); inhibition spontaneous production tumor necrosis factor-alpha (TNF-α)	sarcoidosis
indometacin	pain control	prostaglandin synthesis inhibition	closing ductus botalli immediately after birth
propranolol	angina pectoris, hypertension	beta blocker	infantile hemangiomas
sildenafil	erectile dysfunction	phosphodiesterase inhibition	pulmonary artery hypertension
thalidomide	soporific	sedation immunosuppression immunomodulation anti-inflammatory angiogenesis inhibition	multiple myeloma erythema nodosum leprosum cachexia graft-versus-host disease sarcoidosis

or may induce systematic examination of completely new applications. This may even lead to new licenses or to off-label use being recommended in therapeutic guidelines. There is nothing wrong with this; in fact, it is an efficient way to increase the useful effects of a discovery. Health insurers should not frustrate this natural innovation process by refusing reimbursement. Moreover, it will be more likely that in patients with a rare disease a treatment effect can be achieved although randomised studies are lacking. In these particular disorders the pathophysiological mechanisms that play a part, the knowledge gained from research into other, less rare disorders with a similar pathophysiological mechanism can be used to develop an 'orphan therapeutic indication' (using a common drug for a rare indication).

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