

Drug Rediscovery to Prevent Off-Label Prescription Reduces Health Care Costs: the Case of Tioguanine in The Netherlands

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We have been concerned with drug rediscovery since 2001 at the Gastroenterology unit of the VU University Medical Center [1]. Generic therapy, often successfully used off-label in daily practice and well described in the literature in large observational studies, should be further developed for safe and economically viable use. To prevent off-label use but also to encourage scientific exploration of the potential of available drugs, legislative authorities should stimulate re-registration of these drugs.

Drug Repositioning and Drug Rediscovery

Pharmaceutical companies spend billions of dollars to develop, authorize and launch new drugs. The return on invested capital for developed new drugs fell from nearly 12% in 1995-2000 to 7% in 2009 [2]. As a result, companies have turned to an alternative strategy: Drug Repositioning. Drug Repositioning is the scientific and commercial strategy of taking a known compound and commercializing its use for a new indication through a variety of means (reformulation, delivery method, systematic identification of side-effects). We define Drug Rediscovery as the science dealing with the

use of old active substances to develop new treatments. So far, investments in pharmaceutical innovation are made by industry during the period of patent protection, whereas the horizon of drug use is much longer. This is particularly regretful since this does not stimulate the utilization of the full potential of existing drugs.

Investing in Drug Rediscovery

Currently, the pharmaceutical industry does not invest in off patent drugs; the business model of the pharmaceutical industry does not allow for investing in regulatory development of medicinal products which are not protected, generally by patents. The same goes for the generic companies: so far Drug Rediscovery does not fit in their business models either. In the current paradigm it does not make sense to invest in the clinical development of generic drugs if there is no foreseeable return on investment. Nowadays on-label positioning of off-label medication seems only possible using public sector or healthcare insurance company-supported resources. A global (financial) infrastructure for drug rediscovery has not yet been developed.

Barriers for Drug Rediscovery

In respect of academic endeavors for Drug Rediscovery, scientific research is on the one hand hindered by continuous off-label use and the use of unauthorized medicines, including pharmacists' preparations. Off-label prescriptions hamper proper pharmacovigilance. On the other hand, financial investments to perform research including clinical trials are largely from pharmaceutical industries which, as illustrated above, are reticent as long as there is not a foreseeable return on investment. The aforementioned arguments are the main reason that legislative authorities disapprove the prescription of off-label drugs. In addition to this, most prescribers feel uncomfortable prescribing these "unauthorized" drugs even though they are aware of the potential patient benefits. Moreover, patients are concerned when reading the instruction leaflet, as it does not mention that the drug can be used for their illness.

Examples of Drug Rediscovery

Methotrexate in rheumatoid arthritis has shown robust on-label evidence for efficacy over the years [3]. Aspirin, developed as a painkiller more than 100 years ago, is nowadays widely and successfully used in cardiology and neurology, and can perhaps in the near future be used to decrease the risk of developing cancer [4].

In hepatogastroenterology this drug-repositioning applies to the use of tried drugs such as Tioguanine, an on-label drug for leukemia; cladribine, a cytostatic used on-label for hairy cell leukemia; and cyclosporin used on-label to prevent rejection after transplantation and now used as a rescue therapy in ulcerative colitis, still off-label [5-7].

The case of Tioguanine

When off-label drug usage is prevented or discouraged by legislation authorities and/or is no longer to be covered by the health insurance companies, all that remains in the treatment of inflammatory bowel disease (IBD) is prednisone or much more expensive biologicals as rescue therapy. In The Netherlands an estimated 1,500 IBD patients are currently being treated, off-label, with Tioguanine in tablets of 40mg (Lanvis®) or in capsules of 18, 21 or 24mg (by Pharmacy “Zorg” in Elsloo). Most often it is used as a rescue drug after failure of the conventional thiopurines azathioprine and mercaptopurine [8, 9]. After initial positive reports regarding its efficacy and tolerability profile in the off-label treatment of IBD, other literature emerged regarding the association between Tioguanine and hepatotoxicity [10]. From that point on its use for IBD treatment was largely abandoned. Although the association between the use of Tioguanine and hepatotoxicity is likely to exist, there is evidence that this toxicity is dose-dependent [11, 12]. Using Tioguanine in lower dosages seems to result in an incidence of hepatotoxicity that is comparable to that of thiopurine in naïve IBD patients [13]. Tioguanine doses of around 0.3 mg/kg have been already shown to be safe, although a much larger cohort study including liver biopsies is expected to be published soon [14].

How to make it work for Tioguanine?

One initiative that should be encouraged is to perform a randomized double blind study, azathioprine or mercaptopurine versus Tioguanine, focusing on compliance, side-effects and drug efficacy. We are often reproached for lacking this kind of data. Such a well-powered study would easily cost 700,000 to 1 million Euros. Despite the reduction in the use of biologicals, which could amount to savings of 10-15 million Euros per year in The Netherlands, the funds are simply lacking to process and trace the data of the estimated 1,500 Dutch patients who use Tioguanine (personal communication; Ministry of Health, Welfare and Sports). Since 2009 we have been in constant communication with VWS (Ministry of Health, Welfare and Sports), CBG (Medicines Evaluation Board) and numerous others parties in the field, to consider how the re-registration of these older drugs for new indications could be achieved as a Drug

Rediscovery activity. Re-registration would allow for the evaluation of safety/post-marketing issues. Smaller parties in cooperation with a big generic company in The Netherlands have already succeeded in making pharmacokinetically sound Tioguanine tablets of 10 and 20 mg. We expect those to become available through the pharmacists. If a re-registration “under certain conditions” were achieved, the pharmaceutical industry (Dr Falk®, Ferring®, Abbvie® etc.) would presumably be interested in further research. New product brands are conceivable. Informal discussion with FDA suggests that observational studies would suffice, but so far prospective randomized clinical trials seem to remain required, effectively blocking Drug Rediscovery initiatives.

Drug rediscovery and drug repositioning might be beneficial, not only for patients and prescribers, but also for the pharmaceutical industry and health-care economics. Although legislative authorities encourage drug rediscovery, a solid program to enable funding for research and product protection is missing. To this end it should only be a matter of time for suitable legislative and institutional frameworks to be established in Europe as well as in the US.

Drug repositioning of Montelukast, cladribine, 6-Mercaptopurine and Methotrexate in IBD might be imperative but at this moment this process is hampered by a closing window of opportunity and the lack of global regulations.

Conflicts of interest. No conflict to declare.

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