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SPOTLIGHT COMMENTARY

Spotlight Commentary: What's new in lipid-lowering pharmacology? Integrating basic and clinical research to improve patient outcomes

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Statins have been the mainstay of lipid-lowering therapy since the 1990s, and many people alive and in good health today have statins to thank for their fortunate situation. The very nature of preventative medicine makes it impossible to know which individuals have benefited, but the numbers speak for themselves. Convincing evidence from a multitude of large-scale randomized controlled trials demonstrates that statin therapy reduces the risk of major cardiovascular events by approximately one quarter, for each mmol/L reduction in low-density lipoprotein (LDL), for each year (after the first) for which it is taken.[1]

Recent excitement and discussion in the lipid-lowering field has focused on newer lipid-lowering agents, particularly inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), which result in substantially lower LDL-Cholesterol (LDL-C) than can be achieved with statin therapy. PCSK9 is an important regulator of hepatic LDL receptors. When PCSK9 is inactivated by monoclonal antibodies (MoAbs) (alirocumab and evolocumab) or its production is halted by small interfering RNA (inclisiran), LDL receptors are upregulated, and LDL particles are more effectively cleared from the circulation. This reduces the extent to which LDL-driven atherosclerosis can develop. Large-scale clinical trials have demonstrated the benefits of MoAb PCSK9 inhibitors against major cardiovascular events. Encouragingly, recent research suggests that evolocumab has a similar pharmacokinetic and pharmacodynamic effects in Caucasian and Asian individuals, suggesting that the drug will be useful across a range of populations.[2] Nevertheless, the high cost of new pharmacological agents and the extensive long-term clinical trial evidence for statin therapy means that statins will continue to be the first-line choice of drug in the vast majority of patients for many years. It is essential, therefore, that researchers continue to investigate these life-prolonging drugs, to enable them to be used to optimally benefit patients.

What is left to discover about a class of drugs which is used extensively throughout the world, and which has been in our therapeutic tool-box for over thirty years? Quite a lot, as it happens. As ever, pharmacology leads the way in making discoveries which allow us to improve patient care. The centrality of the dose–response relationship to the understanding of how drugs work was for many years emphasized by the inclusion of a stylized characteristic sigmoidal curve (on an implied linear-log scale) within the logo of the British Pharmacological Society. In preclinical experiments, the biological response to a drug can be carefully characterized across a wide range of concentrations, often in minutes or hours, within model systems. The same is not true for clinical trials which are expensive, and, when they are based on meaningful clinical outcomes, take many years to reveal their answers. In these circumstances, it is rarely feasible to test more than one or two doses of the investigational agent, carefully chosen based upon small dose-ranging studies and pharmacokinetic modelling. The consequences of choosing the 'wrong' dose in clinical trials can be catastrophic: too low, and a potentially therapeutic drug appears ineffective; too high, and the benefits of the drug might be outweighed by toxicity.

[Correction added on 18 September 2020, after first online publication: Article title has been corrected in this online issue version.]

In a thought-provoking recent article, Simon Dimmitt and colleagues from the University of Western Australia apply pharmacological principles to clinical data and argue that our current doses of statins are indeed too high. The authors discuss the relevance of ED50 (effective dose 50, the estimated mean population dose necessary to achieve half the maximum possible drug effect, Emax) in dose-ranging. They point out that in cardiology, drugs are commonly administered at doses which are a few fold higher than their ED50; for example, hydrochlorothiazide is dosed at 2.5× its ED50, with similar ratios for other drugs: amlodipine (5×), metoprolol (3.3×), fenofibrate (1.8×) and clopidogrel (2.5×). Similar ratios are employed with first-generation statins, for example, simvastatin (0.3–5.3×) and pravastatin (0.25–2×). This is in stark contrast to the newer statins, atorvastatin and rosuvastatin, both of which have recommended doses which are up to 40× larger than their ED50 for LDL-C-lowering.[3] The authors persuasively and coherently argue that raising the dose so far above the ED50 predisposes patients to adverse effects without a parallel increase in therapeutic benefit. The reported extent of statin-associated side effects is probably exaggerated, owing to the 'Drucebo' (DRUg + plaCEBO) effect by which well-publicized side effects are attributed to statin therapy, even when there is unlikely to be a causal relationship.[4] However, long-term adherence to statins is poor, and non-adherence is associated with poor clinical outcomes.[1,3,4] Should we suggest lower doses of atorvastatin and rosuvastatin in individuals who experience muscle symptoms, on the basis that some statin therapy is better than none? Such an approach is not necessarily backed by high-quality randomized controlled evidence but is a reasonable approach in light of the arguments made by Dimmitt et al. Interestingly, a meta-analysis of randomized controlled trials found that alternate-day dosing of atorvastatin and rosuvastatin to be as effective as daily-dosing in reducing LDL-C.[5] The International Lipid Expert Panel (ILEP), a collaborative group of physicians and scientists, has made recommendations for the management of statin intolerance which include reducing the dose of statin to that which can be tolerated by the patient.[6]

Variability between patients in the dose of statin which can be tolerated without side effects may reflect inter-individual differences in drug metabolism. Recently, Turner, Pirmohamed, and colleagues from the University of Liverpool investigated factors affecting plasma concentrations of atorvastatin and its metabolites in 571 patients hospitalized for non-ST elevation acute coronary syndrome. In addition to confirming existing known factors, they identified smoking (which reduces hydroxylation and increases lactonization of atorvastatin), proton pump inhibitors and loop diuretics, both of which were associated with increased atorvastatin concentrations. Although such effects were small and potentially dependent on the CYP2C19 phenotype, they may be sufficient to precipitate toxicity in some patients on high statin doses.[7] Their results also highlight the growing importance of considering pharmacogenetics as an aspect of personalized medicine.

Cardio-oncology is an increasingly important field of investigation, as the remarkable increase in cancer survival in recent years raises the question of how to manage cardiovascular risk in individuals who have previously been or are currently being treated for malignancies. This, of course, includes the consideration of drug–drug interactions. Osimertinib is an epidermal growth factor receptor tyrosine kinase inhibitor used in the treatment of non-small-cell lung carcinomas. Based upon its known mechanism of action, theoretical interactions with simvastatin (via CYP3A) and rosuvastatin via (breast cancer resistance protein substrate) have been proposed. Recent phase 1 studies detected no clinically relevant interactions, suggesting that it is safe to use simvastatin (and other CYP3A substrates) and rosuvastatin at the same time as osimertinib.[8] Intriguingly, statin use may be associated with better outcomes in cancer. A meta-analysis of observational studies demonstrated that post-diagnostic statin use was inversely associated with all-cause mortality HR (95%CI) 0.74 (0.63–0.8). Such interesting findings should provoke both randomized controlled trials (to determine whether a causal relationship exists) and experimental pharmacology (to study any underlying mechanisms).[9]

It has long been apparent with respect to LDL-C that 'lower is better'. It is increasingly clear that the magnitude of CVD risk reduction derived from lipid-lowering therapy increases with the duration of therapy; that is, 'lower is better, for longer'.[10] Nevertheless, as is the case for many preventative interventions in health care, concern is often expressed that in translating the results of clinical trials and epidemiological studies into guidelines, we are treating the population, rather than the individual patient. It is also important not to extrapolate beyond the limits of good quality data. It is possible that there is a baseline lower limit of LDL-C required for normal physiological function, although no such limit has been found with current drugs, even at their highest doses. The pharmacological studies briefly described in this commentary all in some way help us to consider a more personalized and patient-centric approach to lipid-lowering therapy so that we will be able confidently to say that 'lower is better, for everybody'.

COMPETING INTERESTS

Dr Penson owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Napp and Sanofi.

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