EDITORIAL

Hyperlipidaemia and monoclonal antibodies – paying for outcome

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The introduction of high-dose statin therapy, more potent statins and the corresponding clinical trial results have led to new treatment targets in secondary prevention of cardiovascular disease (CVD).[1] Most guidelines recommend that for secondary prevention patients require a treatment goal of less than 1.8 mmol/L low-density lipoprotein (LDL)-cholesterol (LDL-C).[2] While the use of high-dose atorvastatin therapy is expected to become more widespread now that atorvastatin is available as a generic drug,[3] in practice, poor compliance seriously impacts effective treatment.[4] Only 1.9% of patients in the Treating to New Targets (TNT) study reduced the randomised treatment of 80 mg atorvastatin to 40 mg,[1] whereas, in practice, the mean dose prescribed is 32 mg per day.[5] For statins, there appears to be a road-block to implementing the results of large randomised-controlled trials (RCTs), similar to the issue of treating hypertension, another 'silent' disease.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new target for the treatment of hyperlipidaemia. PCSK9 is apparently complimentary to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibition with statins.[6,7] Most advanced in the development path are two monoclonal antibodies (mAbs) against PCSK9, alirocumab (SAR236533) and evolocumab (AMG145), both subcutaneous injectable drugs administered at bi-weekly or four-weekly intervals. Both compounds demonstrated solid reductions in LDL-C, however, dose selection for both focused on the most effective dose and did not consider titration according to treated baseline or intended target levels in phase II.[8,9]

Sanofi/Regeneron for alirocumab and Amgen for evolocumab have recently announced that large RCTs with either compound will explore the preventive effect in either post-acute coronary syndrome (ACS) or very high CVD risk populations with low LDL-C, 'likely to be' below 1.8 mmol/L, on cardiovascular morbidity and mortality.[10,11]

Similar patient populations with higher baseline LDL-C levels have been and are being tested in large RCTs with other lipid-lowering drugs, e.g. high-dose atorvastatin, ezetimibe and dalcetrapib.

Results of aggressive LDL-C reduction

The Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL) study was conducted in patients with a history of acute myocardial infarction (MI), 90% of patients within less than two months of randomisation, using a high dose (80 mg atorvastatin) and a moderate dose (20 mg simvastatin) lipid-lowering regimen.[12] Baseline LDL-C was 3.1 mmol/L. The reduction in LDL-C of 0.6 mmol/L resulted in an 11% reduction in the primary composite end point, predominantly by a reduction in non-fatal MI by 17%. The event rates were 10.4% and 9.3% for major coronary events in the placebo and active group, respectively. The rate of non-fatal acute MI was 7.2% and 6.0% in the placebo and active group.

Dal-Outcomes investigated the effect of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib in patients with recent ACS. The primary efficacy end point was a composite of death from coronary heart disease, non-fatal MI, ischaemic stroke, unstable angina (UA), or cardiac arrest with resuscitation. LDL-C at baseline was 1.9 mmol/L. Compared with placebo, dalcetrapib did not alter the risk of the primary end point (cumulative event rate, 8.0% and 8.3%, respectively) and did not have a significant effect on any component of the primary end point or total mortality.[13] Steve Nissen commented that dalcetrapib is a weak CETP inhibitor and that the result is, therefore, not surprising.[14] An alternative explanation would be that the event rates in Dal-Outcomes were too low to detect a meaningful difference in favour of dalcetrapib.

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) was originally designed to randomise 11,000 patients with recent, stabilised ACS to compare two lipid-lowering treatment regimens (simvastatin 40 mg *vs.* simvastatin 40 mg plus ezetimibe 10 mg).

Primary end point is cardiovascular death, non-fatal MI and hospitalisation for UA or coronary revascularisation. Anticipated follow-up is 2.5 years based on a 23.5% event rate in two years in the control arm and a 10% difference in favour of the intervention.[15] The study was initiated in 2005 and enrolment was increased to 18,000 patients by 2008, because the anticipated number of primary events was not attained. Baseline LDL-C was 2.5 mmol/L.[16]

Event rates

Not surprisingly, medical management of patients with coronary artery disease (CAD) has improved. The expected event rate in IMPROVE-IT is identical to the observed event rate in IDEAL, despite a 20% higher baseline LDL-C level in IDEAL. However, in IMPROVE-IT, the primary composite end point includes soft events like hospitalisation for UA or coronary revascularisations. Nevertheless, and based on the update report on IMPROVE-IT, it appears unlikely that the study will be completed successfully. Even if successfully completed with a 10% difference in primary events, it can be anticipated that the difference will be driven by soft events and that the number of patients needed to treat (NNT) to avoid one hard event (cardiovascular death or non-fatal MI) will be too high to justify an intervention in this patient population. Even with higher relative reductions of LDL-C by PCSK9 inhibition, there remains (due to the variability in response of 40–80%) the risk of very low LDL-C levels (below 0.6–0.8 mmol/L) in the absence of the possibility to titrate these drugs according to potential target levels.

There is an ongoing controversy on the value of LDL-C as a surrogate parameter for outcome with other mechanisms of action than statins to reduce LDL-C. This discussion was triggered by the publication of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis Regression) trial,[17,18] a study to assess the effect of ezetimibe on carotid intima media thickening (cIMT), which was negative, i.e. demonstrated no reduction in cIMT, despite a reduction in LDL-C. However, there was no cIMT at baseline, and the study was not designed to demonstrate the effect on progression of cIMT, and there is now clear evidence with the SHARP (Study of Heart and Renal Protection) trial that reducing LDL-C with ezetimibe will result in outcome benefit.[19]

Patients with stable CAD and recent ACS appear to be well treated outside the clinical trial setting, as exemplified with the baseline characteristics of Dal-Outcomes: 98% of patients were on statins with a treated LDL-C of 1.9 mmol/L at baseline. The observed event rates in clinical trials are consequently lower than expected. Although treatment guidelines recommend treated LDL-C values of less than 1.8 mmol/L in this population, the incremental outcome benefit in patients with a baseline LDL-C of 2.6 mmol/L seems marginal and, thus, the number of patients that need to be randomised is very high. This directly impacts, i.e. increases, the number of patients needed to treat and has a huge impact on cost-benefit. NNT for generic atorvastatin ranges between 10 in the highest risk category (five years CVD risk of 40%), and 77 in the lowest risk category (five years CVD risk of 5%).[20]

What is the threshold?

Although the relationship of LDL-C and CVD risk is described as linear, as is the inverse effect of lipid-lowering interventions on CVD risk,[21] it appears likely that there is a lower threshold to either attain or to detect benefit from LDL-C reduction. While data from large RCTs with treated baseline values of less than 2.0 mmol/L are limited, some of the recently completed and ongoing studies indicate that it is difficult to describe the benefit in the context of an RCT. Therefore, performing outcome trials with new lipid-lowering interventions, PCSK9 monoclonals or other new chemical entities (NCEs), in patients with recent ACS requires very careful analysis of expected benefits and risks. The calculation of NNT may provide additional important information on the practicality and the economic feasibility of a new intervention.

Assuming that the average annual treatment costs of PCSK9 mAbs will be 10,000–15,000 EUR (based on the costs of omalizumab,[22] a monoclonal antibody against IgE, for the treatment of asthma),[23] it remains questionable whether an expected marginal reduction in morbidity with a mAb in a relatively low-risk population, based on the possibilities to reduce LDL-C, could justify the reimbursement of this new intervention. An important medical question that remains unanswered after the RITA (Randomised Intervention Treatment of Angina) trials is the long-term value of a coronary intervention compared with aggressive medical therapy. It appears that coronary intervention provides immediate relief of symptoms, without an improvement in long-term prognosis compared with medical therapy.[24,25] The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) study will address this question in approximately 8,000 patients, with a target LDL-C of less than 1.8 mmol/L.[26] With a new intervention, complementary to high-dose statin therapy, that has demonstrated sustained efficacy in phase II clinical trials and could attain much lower LDL-C levels than 1.8 mmol/L, a long-term comparison of coronary intervention versus intensive medical therapy could deliver an argument why another costly medical intervention should be reimbursed while restricting percutaneous coronary intervention (PCI) to symptomatic patients only

Conflict of interest

None declared.

Editors' note

See also the editorial by Peter Sever and Judy Mackay on pages 91–3 of this issue.

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