Marketspace

Dyslipidaemia: Focus shifts from LDL-C to HDL-C

Duncan Emerton

Date Received (in revised form): 19th October, 2006

Duncan Emerton, PhD
has worked as a senior analyst in the Healthcare Competitive Intelligence team and Cardiovascular and Metabolic Diseases team. He has extensive experience in a variety of roles within preclinical and clinical drug development, and has worked for several large pharma and biotech companies. His current areas of focus include commercial and R&D issues in the fields of hypertension (systemic and pulmonary), dyslipidaemia, heart failure and cardiac arrhythmias.

Abstract

In this current analysis of the antidyslipidaemics market, a shift in focus from low-density lipoprotein cholesterol (LDL-C)-targeted therapies to drugs that elevate high-density lipoprotein cholesterol (HDL-C) is described. Key reasons for this evolution are several-fold, but mainly focus on significant generic erosion of LDL-C-targeted therapies, particularly the statins, and loss of revenues therein. Additionally, with LDL-C-lowering efficacy unlikely to improve without sacrificing patient safety, elevating HDL-C has emerged as a therapeutic option in the long-running battle against coronary heart disease.
Journal of Commercial Biotechnology (2007) **13,** 120–124. doi:10.1057/palgrave.jcb.3050039

Keywords: *LDL-C, HDL-C, CETP inhibitor, Apo-A I mimetics, vaccine*

INTRODUCTION

Since the advent of the statin era back in 1994, when the first of many large statin outcome trials were published,[1–3] the reduction of atherosclerotic low-density lipoprotein cholesterol (LDL-C) using orally active HMG CoA reductase inhibitors – the statins – has been shown to significantly reduce cardiovascular mortality and morbidity in a wide variety of patient populations. Despite the benefits of aggressively reducing LDL-C levels with statins during these long-term outcome trials, it must be noted that statins have only managed to reduce cardiovascular risk by 25–33 per cent over the same period. As such, with 66–75 per cent of cardiovascular events not being prevented, the statins have brought us a long way, but not all the way.

Correspondence: Duncan Emerton, PhD, Datamonitor, Charles House, 108-110 Finchley Road, London NW3 5JJ, UK
Tel: +44 (0) 207 675 7245
E-mail: demerton@datamonitor.com

Moreover, additional meta-analyses of recently published statin trials which employed aggressive, high-dose regimens tell us that even when these therapeutic strategies are employed, only minor improvements in cardiovascular risk, compared to standard dose strategies, are seen. Notwithstanding this, statin therapy has been a significant achievement in recent cardiovascular medicine. It is, however, impossible to ignore what the data tells, which is that new therapeutic targets, potentially high-density lipoprotein cholesterol (HDL-C), must be considered as a means of reducing cardiovascular risk even further.

TARGETING LDL-C: THE CURRENT GOLD STANDARD OF CARE

Blocking the formation of endogenous cholesterol via the inhibition of HMG CoA reductase using statins such as atorvastatin (Lipitor; Pfizer), has grown into the gold standard of care for the treatment of hypercholesterolaemia, with many trials

showing that levels of LDL-C are better in reducing cardiovascular risk. On the back of this, the global[4] statins market has grown at a staggering rate over the last decade, culminating in a market value of $23.1bn at the end of 2005, or 86 per cent of the global antidyslipidaemics market.[5] In addition to the statins, another class of LDL-C-targeted therapies, the cholesterol absorption inhibitors have emerged in recent years as a complementary approach to the use of statins in reducing elevated LDL-C levels, as these drugs reduce the amount of exogenous cholesterol the body absorbs from the gut. One example of a drug from this class is ezetimibe (Zetia; Merck/Schering-Plough).

Despite impressive reductions in LDL-C being possible with both statins and cholesterol absorption inhibitors, overall cardiovascular risk has yet to be reduced by more than 30–40 per cent in long-term outcomes studies. This is despite high-dose statin strategies being employed. Moreover, it remains to be seen whether statins, in combination with cholesterol absorption inhibitors can reduce cardiovascular risk to a greater extent than statins alone. Trials such as Merck's IMPROVE IT (*Imp*roved *R*eduction of *O*utcomes: *V*YTORIN *E*fficacy *I*nternational *T*rial) study, which is still recruiting patients, have the potential to answer this question, but data from IMPROVE IT are not expected until early 2009.[6]

HDL-C: THE NEW BATTLEGROUND FOR ANTIDYSLIPIDAEMIC THERAPY?

Large, prospective, epidemiological studies have revealed that low HDL-C is an independent predictive risk factor for coronary heart disease (CHD). Indeed, CHD risk is decreased by around 3 per cent for each increase of 1 mg/ml in HDL-C compared to around 1 per cent for each decrease of 1 mg/ml in LDL-C.[7] Presently, there are three classes of marketed therapies that have been shown to elevate HDL-C; statins, fibrates and nicotinic acid derivatives. Elevations with statins have been shown to contribute significantly to overall event reductions.[1] For fibrates and nicotinic acid derivatives, long-term outcome data for each class are limited, but what trial data do exist reinforces the notion that elevating HDL-C reduces overall cardiovascular event rates compared to placebo.[8,9]

The impact of HDL-C elevating therapies on overall cardiovascular risk, combined with concerns regarding the tolerability of currently marketed products, has stimulated R&D into more effective HDL-C-elevating agents. One novel approach is the cholesteryl ester transfer protein (CETP) inhibitors. CETP acts as a key intermediary in the distribution of cholesterol between HDL-C and LDL-C. CETP inhibitors should, in theory, improve the ratio of HDL-C to LDL-C, the so-called atherogenic index, and thereby slow the development and progression of atherosclerosis. Additionally, reformulation of niacin with agents designed to improve tolerability are currently being investigated. It is, however, the CETP inhibitors that are garnering the lion's share of excitement due to their novel mode of action and potential benefits on reducing cardiovascular risk via elevating HDL-C and regressing atherosclerosis.

THE FUTURE OF HDL-C MANAGEMENT: NEAR-TERM

The most advanced developmental CETP inhibitor is Pfizer's torcetrapib, which is currently in Phase III trials in combination with Pfizer's statin Lipitor (atorvastatin). Pfizer have also recently confirmed that torcetrapib will be marketed as a single pill, but a significant lag period between the combination product and single pill product reaching the market is expected.[10] While torcetrapib is expected to become the first marketed CETP inhibitor, other CETP inhibitors are in development and could potentially compete with torcetrapib in the longer-term (Table 1). Roche is developing small molecule approaches to CETP inhibition (JTT-705; Phase II), while Avant Immunotherapeutics have opted for a biological approach with the development of an anti-CETP vaccine (CETi-1; Phase II).

Results thus far for torcetrapib have been promising. Data presented during the American Heart Association Scientific Sessions

Table 1: CETP inhibitors in development

Drug	Company	MOA	Phase	Comments
Torcetrapib atorvastatin	Pfizer	CETP inhibitor* statin	III	Likely to be first to market; concerning pro-hypertensive side-effect seen in Phase II trials
JTT-705*	Roche	CETP inhibitor	II	Lower potency compared to torcetrapib
CETi-1	Avant	Anti-CETP vaccine	II	Biologic therapy; lack of potency may limit market uptake
BAY-60-5521	Bayer	CETP inhibitor	I	Limited information
JTT-302	Japan Tobacco	CETP inhibitor	I	Limited information

*Exclusive worldwide rights, excluding Japan and Korea, obtained from Japan Tobacco in October 2004.

Source: Datamonitor; Thomson Pharma, Q2 2006, © Thomson Scientific; IMS Lifecycle, © IMS Health, July 2006; MedTRACK, July 2006, © Datamonitor plc; company reported information.

meeting in Dallas in November 2005 demonstrated that a change in HDL-C levels produced by torcetrapib therapy was apparent at week two of a Phase II study, and it remained stable until the end of the study. Torcetrapib alone raised HDL-C by 26–67 per cent. All torcetrapib/atorvastatin combinations produced significant increases in HDL-C by week 12 compared with atorvastatin alone ($p < 0.0001$). The combinations of torcetrapib 60 mg with atorvastatin 10–80 mg raised HDL cholesterol levels by 44–66 per cent ($p < 0.0001$ *v* baseline).

One concern regarding torcetrapib is a reversible, pro-hypertensive side effect discovered during Phase II trials. An analysis of pooled data from ten Phase II trials has shown that subjects who received the 60 mg dose of torcetrapib had a 2 mmHg mean increase in systolic blood pressure (SBP). Moreover, approximately 5 per cent of patients had an elevated SBP of $\geqslant$ 15 mmHg or discontinued study medication due to elevated blood pressure.[11] Despite this, it is expected that this side effect will not ultimately affect the approval of torcetrapib, a belief shared by a US opinion leader who stated that an up-titration of antihypertensive medications while taking torcetrapib, if required, would not overly concern him if there was a significant reduction in the risk of MI, stroke and deaths.[11] Should torcetrapib's Phase III programme be successful, it is expected that torcetrapib will reach the market in 2008.

Data for Roche's JTT-705 show lower potency compared to torcetrapib, with JTT-705 increasing HDL-C by 16–34 per cent at a dose of 300–900 mg. Additionally, JTT-705 decreased LDL-C only in the 900 mg group (−7 per cent) and not in the other groups. By comparison, torcetrapib appears to increase HDL-C and decrease LDL-C levels substantially more than JTT-705. Meanwhile, while data for CETi-1 have shown its ability to elevate HDL-C in patients without cardiovascular disease, comparative efficacy is far lower compared to both torcetrapib and JTT-705, indicating that uptake of this approach may be limited to patients who actively request vaccination rather than becoming a key element in the treatment of low HDL-C. Both JTT-705 and CETi-1 are not expected to reach the market before 2010.

THE FUTURE OF HDL-C MANAGEMENT: LONGER-TERM

Another promising avenue of research that is focused on elevating HDL-C are the use of Apo-A1 mimetics. Research in this field was stimulated by a finding back in the 1970s that a male inhabitant of Limone sul Garda in Northern Italy had low HDL-C, high triglycerides but no cardiovascular disease[12] due to a genetic mutation in the gene that

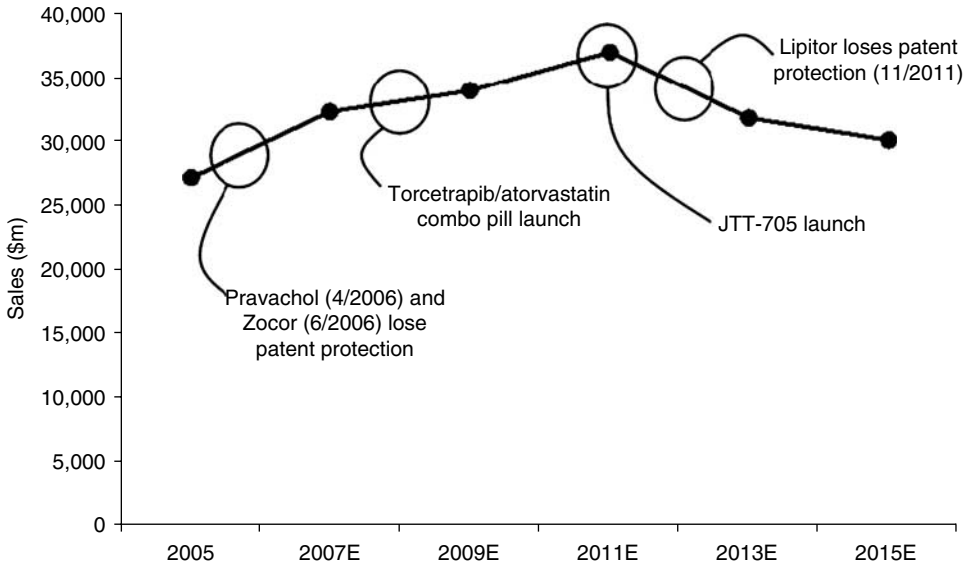

Figure 1: Projected growth, and subsequent decline, of the global antidyslipidaemics market. *Source*: historical sales data from IMS MIDAS sales data; IMS Health, March 2006; forecasts from Datamonitor research

produces Apo-A1 (gene which encodes apolipoprotein A-I, which is the major protein component of in plasma). Since then, Pfizer have taken on the development of the most advanced Apo-A1 mimetic, ETC-216, via its acquisition of Esperion in February 2004.

ETC-216 is a synthetic variant of HDL-C and is currently undergoing Phase II clinical trials. Results thus far for ETC-216 have been promising, and since the publication of a Phase II trial that demonstrated ETC-216's ability to reverse the formation of atherosclerotic lesions,[13] immense scientific, media and financial interest has followed the clinical development of this product. The primary outcome measure from this trial was the change from baseline in percentage atheroma volume, as measured by intravascular ultrasound (IVUS). Results showed that five weeks of treatment with ETC-216 produced a significant 4.2 per cent reduction in atheroma volume ($p < 0.01$). While these results are encouraging and potentially very exciting, as regression of plaque remains the holy grail of atherosclerosis research, the commercial potential of ETC-216 is limited due to its intravenous route of administration. As a result, it is expected that ETC-216's use will be limited to the acute setting in order to reduce plaque burden, after which time patients will be switched to orally active, chronically administered treatments such as statins and CETP inhibitors.

Perhaps the most exciting member of this new class of HDL-C-targeted therapeutics is Novartis's APP018 (formerly known as D-4F). APP018, in-licensed from Bruin Pharmaceuticals in late 2005, is an orally bioavailable, 18 D-amino-acid peptide derived from the Apo-A1 sequence. Its key mechanisms of action include binding to lipids and native HDL-C, thereby driving the formation of antiatherosclerotic pre-HDL-C by remodelling the existing HDL-C pool.[14] The commercial potential for APP018 is significant, primarily due to its orally active formulation and its ability to improve the quality of antiatherosclerotic HDL-C rather than simply the quantity. Currently in Phase I trials, APP018 is not expected to reach the market before 2015, and perhaps even later.

FUTURE OUTLOOK

Despite the launch of novel therapies that target HDL-C via inhibition of CETP and via promotion of HDL synthesis, sales growth for the global antidyslipidaemics market is expected to be flat between 2006 and 2015[11] (Figure 1). Key resistors to growth include the loss of US patent protection for Merck & Co.'s Zocor (simvastatin) and BMS's Pravachol

(pravastatin) in 2006 and for Pfizer's Lipitor (atorvastatin) in 2011.

Meanwhile, pipeline CETP inhibitors and Apo-A1 mimetics, such as Pfizer's torcetrapib and ETC-216, and a range of lifecycle management strategies for currently marketed products are expected to make up for some loss in value, but not all. In the longer-term, the use of biological approaches in the prevention of cardiovascular diseases, such as dyslipidaemia and hypertension, holds much promise. Should it be possible to develop a vaccine to prevent the development of chronic disease, issues surrounding patient compliance to pill-based therapies will cease to be an issue. To compete effectively, however, safety and efficacy concerns regarding biological therapies need to be addressed.

References

1. Scandinavian Simvastatin Survival Study Group. (1994). Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* **344**, 1383–1389.
2. West of Scotland Coronary Prevention Group. (1996). West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet* **348**, 1339–1342.
3. Cholesterol Treatment Trialists' (CTT) Collaborators. (2005). Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* **366**, 1267–1278.
4. Global in this context refers to the seven major pharmaceutical markets – US, Japan, France, Germany, Italy, Spain, UK.
5. MIDAS sales data, © IMS Health, March 2006.
6. Merck & Co. Press release; 15th November, 2005.
7. Chapman, M. J., Assmann, G., Fruchart, J. C., Shepherd, J., Sirtori, C. & for the European Consensus Panel on HDL-C (2004). Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid – a position paper developed by the European Consensus Panel on HDL-C. *Curr. Med. Res. Opin.* **20**, 1253–1268.
8. Robins, S. J., Collins, D., Wittes, J. T., Papademetriou, V., Deedwania, P. C., Schaefer, E. J., McNamara, J. R., Kashyap, M. L., Hershman, J. M., Wexler, L. F., Rubins, H. B. & for the VA-HIT Study Group (2001). Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* **285**(12), 1585–1589.
9. Canner, P. L., Berge, K. G., Wenger, N. K., Stamler, J., Friedman, L., Prineas, R. J. & Friedewald, W. (1986). Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J. Am. Coll. Cardiol.* **8**(6), 1245–1255.
10. *New York Times*; 26th July, 2006.
11. Commercial Insight – Antidyslipidemics (DMHC2217); published 27th July, 2006; Datamonitor plc., London, UK.
12. www.csmc.edu/pf_6189.html; Cedars-Sinai Heart entre: Apo-A1 Milano; accessed 28th September, 2006.
13. Nissen, S. E., Tsunoda, T., Tuzcu, E. M., Schoenhagen, P., Cooper, C. J., Yasin, M., Eaton, G. M., Lauer, M. A., Sheldon, W. S., Grines, C. L., Halpern, S., Crowe, T., Blankenship, J. C. & Kerensky, R. (2003). Effect of recombinant Apo A-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* **290**(17), 2292–2300.
14. Novartis Pipeline Presentation; September 2005 (online at http://novartis.com/downloads/04_Hughes_Print_london.pdf). Accessed on 28th September, 2006.