

Obstacles and options in the quest for drug candidates against vascular disease

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Summary

The difficulties in cardiovascular drug development have been exposed by recent clinical trials, which have uncovered various limitations of promising drug candidates. Yet, the imperative to improve medical treatment of atherosclerosis in aging populations afflicted by metabolic disease remains unbroken. Herein alternatives to metabolically active compounds such as glitazones and torcetrapib are introduced and discussed, namely CC chemokine receptor 5 (CCR5) antagonists recently

approved for treatment of patients with human immunodeficiency virus-1, interceptors of proatherogenic chemokine interactions, and actively protective pathways. A combination of different strategies may yield improved safety profiles of these therapeutics.

Keywords

Atherosclerosis, chemokines, drug design

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Introduction

Several recent examples (► Table 1) impressively illustrate the inherent risks, pitfalls and limitations of drug development in the cardiovascular arena beyond the ever more established benefit of statins in preventing cardiovascular events in patients with hyperlipidaemia or inflammatory markers (1). A cardiovascular outcomes trial that randomised patients with type 2 diabetes to receive rosiglitazone or alternative diabetes therapies (RECORD) revealed that addition of rosiglitazone to glucose-lowering therapy increased the risk of heart failure, mainly in women (2). While remaining inconclusive about possible effects on myocardial infarction, most likely due to an unusually low event rate, rosiglitazone did not appear to increase the risk of cardiovascular morbidity or mortality over standard glucose-lowering drugs. This result was in discord with a meta-analysis of 42 randomised clinical trials (3), which showed a significant increase in the risk of myocardial infarction associated with rosiglitazone and, despite a lack of access to original source data, indicated potentially severe adverse cardiovascular effects of rosiglitazone. Absence of independent access to all trial data may thus preclude sufficient transparency for physician-scientists to allow unbiased assessment. Consequently, the Food and Drug Administration (FDA) has announced an imminent Advisory Panel to commend whether to remove rosiglitazone from the market (4). Pioglitazone, another thiazolidinedione, despite lowering cardiovascular risk in diabetic patients has also been

associated with serious heart failure (5), hinting at a spectrum of adverse effects shared by this class of drugs.

Recent history of therapeutic limitations

With regards to off-target effects, it is notable that other drugs also yielded ambiguous results. For instance, use of the selective cannabinoid type 1 receptor antagonist rimonabant in patients with abdominal obesity and metabolic syndrome failed to favourably influence the progression of coronary artery disease, as measured by percent atheroma volume, whereas psychiatric adverse effects were more common (6). Similarly, the cholesteryl ester transport protein (CETP) inhibitor torcetrapib, which elevates high-density lipoprotein (HDL)-cholesterol and decreases low-density lipoprotein (LDL)-cholesterol, failed to limit progression of coronary atherosclerosis at lower doses, inducing regression only at the highest HDL-cholesterol levels (7, 8). However at the highest dosage, torcetrapib raised serum sodium and lowered potassium, consistent with an aldosterone-like effect (8). This explains a lack of benefit in the full study cohort but also implies that inhibitors devoid of this off-target toxicity still harbour the potential to halt plaque progression. In the BARI 2D trial, no difference in the rates of death or major cardiovascular events was observed between patients with type 2 diabetes undergoing prompt revascularisation

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Compound	Limitation and option	Current status	Ref.
Rosiglitazone	Higher rate of MI and/or serious heart failure	FDA-approved	2, 3
Rimonabant	Cannabinoid type 1 receptor antagonist Psychiatric adverse effects	Phase II (halted)	6
Torcetrapib	CETP inhibitor Increase in blood pressure, Aldosterone-like effect	Phase III (halted)	7, 8
Darapladip	Lipoprotein-associated PLA2 inhibitor Decreased inflammatory markers Prevented necrotic core expansion	Clinical phase II	26
A-002	Secretory PLA2 inhibitor Reduced PLA2 group IIA concentration suggesting anti-atherosclerotic activity	Clinical phase II	26
Maraviroc	Safe and efficient antagonist of proatherogenic CCR5 receptor	FDA-approved for HIV infection	12, 13
CKEY2	Safe and efficient antagonist of proatherogenic chemokine interaction	Pre-clinical, phase I	18
miR-126	Small RNA displaying profound atheroprotective activity	Pre-clinical	24

Table 1: Examples for obstacles and options in cardiovascular drug development.

and those undergoing medical therapy or between strategies of insulin sensitisation vs. provision (9). These largely disappointing outcomes clearly mandate intensified efforts to discover drug candidates optimally amending medical treatment of cardiovascular disease (10).

Promising experience with a CCR5 antagonist in HIV-1 trials

Given the prominent role of the CC chemokine receptor 5 (CCR5) in atherosclerosis (11), an intriguing development comes from the recent FDA approval of maraviroc, a spiro-diketopiperazine CCR5 antagonist, for clinical use in patients with human immunodeficiency virus type 1 (HIV-1). The safety and efficacy of maraviroc as an antagonist against the HIV-1 co-receptor CCR5 was confirmed in two phase-3 randomised, placebo-controlled trials (MOTIVATE 1 and 2). Eligible subjects had evidence of resistance to drugs from three antiretroviral classes or were triple-class experienced, had plasma HIV-1 RNA levels >5,000 copies/ml and R5 virus only (12). Patients were randomly assigned to placebo or maraviroc once or twice daily and received optimised background therapy based on drug-resistance testing and treatment history. As compared with placebo, maraviroc resulted in significantly greater suppression of HIV-1 with plasma RNA reduction below 50 copies/ml and greater increases in CD4 cell counts at 48 weeks. The frequency of adverse events was similar among all groups, except a significant increase in oesophageal candidiasis with maraviroc once daily. The treatment benefit extended to all subgroups, while virologic failure of maraviroc was associated with emergence of CXC chemokine receptor 4 (CXCR4)-using virus but no evidence of a decrease in CD4 cell count (13).

Thus, while targeting CXCR4 has proven to be more challenging, antagonists against the powerful proatherogenic receptor CCR5, such as maraviroc, vicriviroc (in phase-3 trials) or others in development harbour significant benefit and documented safety in clinical trials (14). Increased atherosclerosis associated with HIV infection has been reported to occur in the absence of antiretroviral therapy, overt viraemia or immunodeficiency, implicating chronic inflammation to account for early atherosclerosis in these patients (15). In this context of susceptibility, it would be well warranted to evaluate the effects of maraviroc on plaque progression and cardiovascular events in a controlled trial enrolling patients with HIV-1 and coinciding coronary artery disease, thereby aiming to kill two birds with one stone (16). As the issue of safety has been well addressed in recent trials and the crucial role of CCR5 provides reasonable mechanistic grounds, it would be interesting to embark on randomised controlled trials examining the antiatherosclerotic properties in this group of patients.

Alternatives with improved safety profile

An important caveat for the chronic use of CCR5 antagonists arises from studies in subjects with the CCR5 $\Delta 32$ mutation or using the receptor antagonist Met-RANTES, which unveiled profound immunologic effects associated with more severe infection and mortality from West Nile virus or impaired clearance of herpes-simplex virus (HSV) infection (17, 18). Although congenital deficiency may not be equivalent to blocking the CCR5 receptor with a peptide or small-molecule inhibitor; this underscores the need for careful long-term safety monitoring. In turn, this prompted us to introduce a highly selective approach to suppress the atherogenic and inflammatory functions of the CCR5 ligand CCL5 without clinically relevant side-

effects. The underlying principle is based on the chemokine interactome, which provides a new level of functional plasticity and regulatory control in the chemokine system (19). The disruption of heteromer formation of the platelet-derived chemokines CCL5 and its interaction partner CXCL4 using a cyclic peptide inhibited their synergy in inflammatory cell recruitment (18, 20). Treatment with the peptide resulted in a marked inhibition of atherosclerosis and inflammatory cell content but did not interfere with normal immunological responses, e.g. macrophage-mediated HSV clearance or T-cell function (18). The compound termed CKEY2 is currently undergoing extensive toxicological testing and preparation for clinical phase trials in cardiovascular outcome studies (10).

Conversely, reciprocal options for limiting plaque progression aim at increasing the expression of chemokines, e.g. the CXCR4 ligand CXCL12, which have been linked to plaque stabilisation and atheroprotection (21, 22). Along these lines, reduced atherosclerosis in mice treated with rosuvastatin as an established drug is associated with up-regulation of CXCL12 and increased influx of regenerative progenitor cells into the lesions (23). Similarly, miR-126 enriched and delivered by endothelial microparticles has been found to unlock a RGS16-restricted autoregulatory feedback loop leading to CXCL12 expression and thereby mediates CXCR4-dependent atheroprotection and plaque stability (24). Notably, expression of CXCL12 on circulating platelets has been reported to be increased in patients with acute coronary syndrome, where it correlates with the number of CD34⁺ progenitor cells (25). This further underscores that CXCL12, e.g. derived from platelets, may play an important role in peripheral homing of circulating progenitor cells and tissue regeneration in a clinical context.

In conjunctive prospect, it can be anticipated that compounds such as new generation CETP inhibitors will be further refined, others, such as phospholipase A2 inhibitors, currently undergoing early clinical phase trials (26) will be compared in larger scale trials, and new promising targets emerge to be validated. Combining new biologicals, such as CKEY2, with small-molecule CETP or other inhibitors at lower doses might not only create a safer profile but beyond increasing therapeutic efficacy towards the main indication, i.e. atherosclerosis or its sequelae, namely atherothrombosis and myocardial ischaemia-reperfusion injury (27, 28), might also be protective against side effects experienced with the small molecules.

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