Introduction and objectives

Cigarette smoke (CS) is causally linked to the development of cardiovascular disease (CVD) through different pathophysiological pathways, which include endothelial injury and dysfunction, oxidative stress, a procoagulatory status, inflammation, and an abnormal lipid profile, all contributing to the development of atherosclerosis.

Toxicant harm reduction, by substituting cigarettes with less-harmful products, is a complementary approach to current tobacco control strategies for smokers who would otherwise continue to smoke. The Tobacco Heating System (THS) 2.2 is a novel tobacco product that heats tobacco instead of burning it, never allowing the temperature to exceed 350°C, thereby preventing the combustion process from taking place and producing substantially lower levels of toxicants (on average more than 95%) compared with CS. In particular, the levels of eight cardiovascular toxicants (acrolein, benzanthracene, benzene, butanaldehyde, hydrogen cyanide, lead, phenol, propionaldehyde) are reduced by ~90% in THS aerosol versus CS. Furthermore, THS aerosol does not contain the solid carbon-based nanoparticles (CNBPs) that are generated by combustion.

Adhesion of monocytes to human coronary arterial endothelial cells (HCAEC), a critical stage in atherosclerosis – THS 2.2 vs. CS (in vitro adhesion assay)

Cell exposure to 3R4F reference cigarette or THS 2.2 aqueous smoke/aerosol extract (smoke/aerosol+bubbled phosphate-buffered saline [PBS]) to PBS or PBS in two hours. Both media were frozen.

Treatment of HCAECs

Indirect and direct treatments: 24-hour-starved HCAECs were treated with thawed conditioned and unconcentrated media for four hours. Fresh direct treatment: 24-hour-starved HCAECs were exposed to freshly generated 3R4F or THS 2.2 a/bPBS (PBS) or PBS for four hours. HCAECs and MMW lysates were collected and stored at –40°C for RNA extraction.

Adhesion assay

Untreated HCAECs and four-cell-treated HCAECs were nuclear stained for 15 minutes and then incubated together for 45 minutes. After cell fixing and washing, remaining adherent MMW and HCAEC cells were counted, and adhesion rate was calculated.

In vitro study to investigate atherosclerotic plaque of the aortic arch

This study examined the development of the hallmark of CVD in ApoE mice chronically exposed to 3R4F CS. THS 2.2 aerosol (matched to the nicotine concentration in 3R4F CS [50 μg/ml]) or PBS for three hours per day, five days per week, for up to eight months (approximately 40% of life).

After two months of exposure to 3R4F CS, mice were switched to THS 2.2 aerosol (switching), filtered air (cessation), or continued exposure to 3R4F CS. The exposure dose corresponded to ~30 cigarettes per day in human comparison.

Conclusions and discussion

The results of the THS 2.2 assessment program demonstrate that:

- THS 2.2 aerosol contains no CNBPs. Additionally, cardiovascular toxicants are reduced by ~90%.
- The adhesion of monocytes to HCAECs in vitro is significantly reduced following THS 2.2 treatment compared with exposure to 3R4F CS.
- Switching to THS 2.2 halted the progression of CS-induced atherogenic changes in vivo.
- In humans, all co-primary endpoints representative of different pathophysiological pathways leading to atherosclerosis shifted favorably, in the same direction as the smoking cessation effect observed in the literature, after six months of switching from cigarettes to THS 2.2.

Pfizer has completed 18 non-clinical studies and 10 clinical studies, including the studies presented here. The evidence available to date indicates that switching to THS presents less risk of harm and has the potential to reduce the risk of smoking-related diseases, such as CVD.

As a next step, Pfizer will complement this THS assessment program with cardiovascular outcome studies intended to demonstrate the clinical benefits of switching to THS (e.g., reduction in the risk of cardiovascular death, myocardial infarction, and stroke) as compared with continued smoking and aiming to improve primary and secondary prevention in clinical practice.

References


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