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Review article

Non-invasive imaging of atherosclerosis regression with magnetic resonance to guide drug development

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ABSTRACT

Slowing of progression and inducing the regression of atherosclerosis with medical therapy have been shown to be associated with an extensive reduction in risk of cardiovascular events. This proof of concept was obtained with invasive angiographic studies but these are, for obvious reasons, impractical for sequential investigations. Non-invasive imaging has henceforth replaced the more cumbersome invasive studies and has proven extremely valuable in numerous occasions. Because of excellent reproducibility and no radiation exposure, magnetic resonance imaging (MRI) has become the non-invasive method of choice to assess the efficacy of anti-atherosclerotic drugs. The high accuracy of this technology is particularly helpful in rare diseases where the small number of affected patients makes the conduct of outcome-trials in large cohorts impractical. With MRI it is possible to assess the extent, as well as the composition, of atherosclerotic plaques and this further enhances the utility of this technology.

1. Introduction

Drug discovery and development follow a complex and long pathway that often does not lead to a commercially viable product. As the cost of drug development burgeoned to prohibitive levels over the past few decades, investigators and industry have looked for ways to curb expenses and increase efficiency minimizing possible failures. The development of new drugs to treat atherosclerosis is often met with the requirement to conduct lengthy outcome trials at extraordinary costs. To limit the possibility of failing to attain the desired outcome after having conducted a phase-3 trial, investigators have utilized surrogate targets that provide information on the burden and composition of atherosclerotic plaques [1–3]. Particularly challenging is the development of drugs for rare diseases, where conducting randomized outcome trials is hampered by the limited number of patients affected by the condition under study. In this light, atherosclerosis imaging has provided intermediate goals to test effectiveness of novel treatments [4–6]. There are indisputable advantages in using imaging endpoints. For example, while in mortality and morbidity trials the endpoint is only provided by patients who experience an event, in trials based on imaging biomarkers the endpoint is provided by every patient. This increases the statistical power of the study, thus leading to a reduction in the number of patients compared to event driven trials (tens or hundreds rather than thousands of subjects) and shorter follow-ups (6–24 months rather than 4–6 years). Given its potential impact on drug development, atherosclerosis imaging has been the focus of intense debate and growing interest among scientists, industry and regulators alike. In this paper we review the state of the art of magnetic resonance (MR) for vascular imaging, with a specific focus on its implementation in the process of drug development. Magnetic resonance imaging can provide information on the location, extent and composition of atheromatous plaques in peripheral arterial beds and has been used in numerous trials to study regression of atherosclerosis. However, to date MRI has demonstrated no utility to image coronary artery atherosclerotic plaques.

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2. Imaging biomarkers and their utility

Atherosclerosis is mostly a silent disease and autopsy studies revealed that it is already present in youth [7]. Because of its silent development its first manifestation is often a sudden and unheralded event. This induced scientists and physicians to develop a number of algorithms to estimate risk of events and stimulated the development of a large array of biomarkers and imaging modalities to assess the presence of atherosclerosis and its progression. The earliest attempts at measuring atherosclerosis progression were accomplished with invasive coronary angiography [8–11]. Several studies demonstrated a powerful reduction in event rates with even minimal regression of luminal narrowing with various interventions [12]. Non-invasive imaging modalities were then tested to measure change in atherosclerotic plaque burden or composition and became rapidly popular as a means to test drug efficacy. Like any other biomarker, an imaging marker needs to meet methodological and regulatory requirements to provide acceptable outcome parameters.

Several approaches to biomarker validation have being taken. The NIH Definition Working Group [13] defines a 'biomarker' as follows: 1. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Boissel and co-workers proposed a framework to describe the scientific validity of laboratory parameters for biological outcomes [14]. They posed three stipulations. First [*availability and convenience*], "although the surrogate endpoint should be easier to assess than the corresponding clinical endpoint, the most important advantageous characteristic of the biomarker is its potential to detect the disease process in its earlier stages, resulting in a higher frequency of detection of the disease than the corresponding clinical endpoint". Consequently, validated biomarkers provide early and specific prediction of risk that allows implementation of preventive strategies. For an imaging biomarker to provide relevant data, availability of the imaging device in close proximity to study subjects is essential. Second, there should be a causal relationship between surrogate and clinical endpoint, both quantitatively and qualitatively, through epidemiological studies. Third, it should be possible to estimate the clinical benefit derived from a reduction in the incidence of the surrogate endpoint. A surrogate outcome must meet certain statistical criteria [15], such that it would allow mathematical modeling of a disease process and its consequences. Finally, to become an *accepted* outcome measure to evaluate efficacy of pharmaceutical products in clinical trials, regulatory acceptability must be met.

3. Agencies' acceptance of markers of disease

Acceptance of surrogate markers (whether "biomarkers" or others) has long been hotly debated and opinions have swayed both in favor and against (some examples are change in CD4 cell count in HIV infected patients, change in PSA levels in prostate cancer and blood pressure measurements in cardiovascular health). In many cases there has been deep disagreement regarding the relevance of a surrogate endpoint. Progression free survival in oncology is hotly debated and it is not clear if the answer is a simple dichotomous "yes or no" but, rather, it might be cancer-specific. It is likely that surrogacy might also be drug-specific and the mechanism of action of one therapy to treat a particular disease might allow one marker as a reliable surrogate for drug alone and not another one intended for the same disease state. Therefore, regulators have been cautious about declaring any particular marker as an accepted surrogate. There are several examples where a compromise had to be reached. In terms of safety, it is often accepted to study "only" a few thousand patients in clinical trials, even though we know that databases of this size are unlikely to identify adverse reactions (possibly severe reactions) that occur in 1 in 1000 or more patients. Similarly, in terms of efficacy, it is often accepted to "only" study treatments for up to 1–2 years, even though they might represent life-long treatments. Clearly, these are examples of regulators being pragmatic and recognizing that the value of making new therapies available sooner, outweighs the risk involved. Other clear examples of pragmatism are in the orphan drug space where reality often dictates the need for flexibility. Such flexibility may relate to the size of the clinical database presented for review (number of patients, duration of follow-up, number of studies, etc.) but also on choice of endpoints. In terms of size of database, for new products entering Phase III trials from 1 January 2000, an average of 731 patients were enrolled in orphan drug trials versus 3540 in non-orphan drug trials [16].

Clinical relevance of endpoints is important but so is the ability to study those endpoints in small clinical development programmes. The CHMP (Committee on Medical Products for Human Use) Guideline on Clinical Trials in Small Populations (Section 4) [17] acknowledges that: "Time to disease progression is an endpoint of intermediate level and it requires a measure of disease severity or of disease progression. *Ideally*, *this should be validated* as a tool for use in clinical trials, but *it is recognised that there might be too few patients to use some for validating endpoints and others for testing treatments*. … It is *preferable*, to be able to identify a causal relationship between treatment and a particular (beneficial) outcome." Hence the acknowledgement that there is an "ideal" and "preferable" way to proceed, but it may not be always possible.

Three questions should be considered; (1) can a study with a "highly preferred" endpoint be conducted? ("highly preferred" might mean preferred by the regulators, and/or an obvious clinical endpoint); (2) is such an endpoint absolutely necessary in order to determine the clinical value of a therapy? and (3) is it actually desirable to use the "highly preferred" endpoint, or would a more efficient trial better serve the public health interest? To this end, intravascular ultrasound (IVUS) and MRI studies offer the opportunity to pursue more efficient endpoints (i.e. smaller trial sizes, with shorter duration and good level of assurance over the results) than more traditional "established clinical endpoints". At the same time they may provide enough information to inform a decision to pursue larger clinical trials or whether such trials should be stopped [18].

4. Atherosclerosis imaging for plaque regression: A historical perspective

Invasive and non-invasive imaging has been used extensively to study progression of atherosclerosis. A few pivotal principles govern sequential imaging of atherosclerosis to assess its temporal changes [1]. First, the test-to-test variability should be smaller than the change detected with sequential imaging. Second, the measured change should be clinically relevant and associated with meaningful outcomes. Atherosclerosis imaging began with quantitative invasive coronary angiography (QCA) [8–11]. Although QCA is not an atherosclerosis imaging technique per se, as it assesses the degree of luminal stenosis but not plaque volume and composition, it demonstrated that even minimal regression or slowing of progression of intraluminal coronary artery disease are associated with a large reduction in event rates [12]. Despite its success, QCA is limited by its invasive nature, the need to use iodinated contrast media and the exposure of patients to ionizing radiation and is therefore not fit for population studies. This stimulated and facilitated the development of non-invasive imaging modalities to detect atherosclerosis and study its progression. Pignoli et al. [19]