Review of: "mRNA: vaccine or gene therapy? The safety issues of regulation"

Kenneth Lundstrom

Potential competing interests: No potential competing interests to declare.

Regulatory Issues Concerning mRNA Vaccines and Gene Therapy

Kenneth Lundstrom

PanTherapeutics, Lutry, Switzerland

Abstract

Concerns related to the development, manufacturing, and regulatory issues for current mRNA-based COVID-19 vaccines have been addressed. Although certain relaxation has been associated with mRNA-based vaccines, they have been subjected to rigorous clinical evaluation in a large number of clinical trials in hundreds of thousands of healthy volunteers. Although there was an urgent demand of COVID-19 vaccines the interpretation that the procedure was too fast to be safe is incorrect. Moreover, the claim that mRNA-based vaccines are relying on untested novel technologies is false as preclinical proof-of-concept studies were conducted in the early 1990s and mRNA vaccines have been subjected to clinical trials against both infectious diseases and cancer more than 10 years ago. On the other hand, there is discrepancy in regulatory issues related to the definition of mRNA-based vaccines, their manufacturing and approval between regulatory authorities. For example, cancer vaccines have been categorized as gene therapy medicinal products (GTMPs), while vaccines against infectious diseases have been excluded. These issues need to be clarified to provide better possibilities for global development and handling of mRNA-based vaccines.

Introduction

The recent publication by Dr. Banoun titled “Regulatory Issues Concerning mRNA Vaccines and Gene Therapy” in Qeios [1] addressed points of great importance related to the current boom in the development of mRNA-based vaccines in the fight against the recent COVID-19 pandemic [2]. The publication strongly focuses on how vaccines are not subjected to similar regulatory evaluation as gene therapy products. Moreover, the author insists that as mRNA vaccines represent a new class of vaccines based on several novel technologies, they should be subjected to more rigorous evaluation than conventional vaccines. According to Dr. Banoun, there is also certain confusion between the World Health Organization (WHO), the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and even the mRNA vaccine manufacturers such as Moderna and BioNTech-Pfizer related to the definition of gene therapy products. The author further claims that it cannot be justified that mRNA-based vaccines are not subjected to studies on specific toxicity of

expressed antigens, potential chromosomal integration, germ-line transmission, reproduction toxicity, and excretion into the environment. Although most of the writing is based on facts and there is an urgent need of improvement and coordination of regulatory procedures of vaccines, particularly mRNA-based vaccines, certain feedback is justified. This is especially timely due to the recent breakthrough experienced for mRNA-based vaccines in the context of the recent COVID-19 pandemic. The aim here is to specifically discuss mRNA-based vaccine development and the reasons behind the current confusion related to their regulatory handling.

History of mRNA-based Vaccines

Throughout her publication, Dr. Banoun drives the message of the novelty of mRNA-based vaccines and how there is insufficient information available to use them safely in humans [1]. However, this information is incorrect as research on mRNA-based delivery systems and vaccine development have been conducted for more than three decades [3]. This is also reflected by the more than 10,000 publications found in a PubMed search using “mRNA-based vaccines” for the search. For example, successful transfer of both plasmid DNA and *in vitro* transcribed RNA into mouse muscle provided expression of the encoded protein in mice in 1990 [4]. Two years later it was demonstrated that intrahypothalamic injection of vasopressin mRNA resulted in reversal of diabetes in rats [5]. Moreover, during the 1990s it was shown that mRNA could be used for vaccine development against infectious diseases [6] and cancer [7]. In the context of clinical settings, a multitude of clinical trials have been conducted for mRNA-based therapeutics already more than 10 years ago [8]. For example, for infectious diseases application of mRNA-based dendritic cells (DCs) elicited potent antiviral T-cell responses in HIV patients [9]. Moreover, mRNA-based expression of Tat, Rev, and Nef in DCs induced specific $CD4^{+}$ and $CD8^{+}$ T-cell responses although no clinical improvement was achieved in a phase I/IIa immunotherapy study in HIV-1 patients [10]. In the case of cancer immunotherapy, melanoma patients have been subjected to direct mRNA injections in a phase I/II trial showing complete response in one out of seven patients [11]. Moreover, intradermal injection of mRNA expressing tumor-associated antigens (TAAs) showed clinical responses in renal carcinoma patients in a phase I/II study [12]. For this reason, it is absolutely incorrect and irresponsible to claim that mRNA-based technologies are new as there are more than 30 years of experience from preclinical studies in animal models and more than 10 years since the first clinical trials were conducted in humans, showing excellent safety, tolerability, and efficacy. Obviously, the strategy and execution of the development of the current COVID-19 vaccines, where the process from identification of SARS-CoV-2 to granting of emergency use authorization (EUA) took approximately one year were unprecedented. These efforts were only possible through the incredible collaboration of research institutes, the biotech industry and governmental and regulatory organizations developing an overlapping strategy for the preclinical research and clinical testing WITHOUT jeopardizing vaccine safety. It is also necessary to take into account that the increasing numbers of SARS-CoV-2 infections and casualties from COVID-19, lockdowns, and socio-economics tragedies caused an urgency for the global community to react. Despite any disinformation/misinformation presented by the aggressive anti-vaccination community, without doubt the COVID-19 vaccines have saved millions of lives and allowed the return to more or less normal life as we knew it before the onset of the pandemic.

Clinical Evaluation of mRNA-based COVID-19 Vaccines

Another claim presented by Dr. Banoun relates to the insufficient assessment of environmental risks, characterization of raw materials and products, and manufacturing methods including control and stability, toxicology, pharmacokinetics, pharmacodynamics, safety, and efficacy. Although certainly due to the tight schedule, it has not been possible to carry out extensive long-term clinical follow-up studies, all seriously developed COVID-19 vaccines, including mRNA-based, viral vector-based, and inactivated whole virus vaccines, have been subjected to government approved and controlled clinical evaluation. Today, the number of clinical trials conducted for mRNA-based COVID-19 vaccines alone surpasses the number of studies for any other vaccine developed. Hundreds of thousands of volunteers have taken part in these trials. Moreover, the administration of more than 13 billion doses of COVID-19 vaccines, including all types of vaccines, the mass vaccination has provided the opportunity to evaluate vaccine safety and efficacy at a scale never experienced before. Naturally, at this scale adverse events have been reported, but in contrast to the misinformation spread on social media, the side effects are generally mild and although serious adverse events have been detected, these are rare and clearly the benefit of vaccination outweighs the risks [13].

Discrepancy Related to Regulatory Issues

Importantly, Dr. Banoun brings to the attention the current problematic and confusing situation of regulatory classification of vaccines and gene therapy products. In this context, mRNA-based vaccines developed against infectious diseases and cancers have been placed in different categories [14]. In this context, cancer vaccines have been categorized under gene therapy medicinal products (GTMPs), while vaccines against infectious diseases have been excluded. This might seem confusing and even strange as the basic technology is the same and both belong to the group of immunological medicinal products. However, the cancer vaccine approach is relatively new compared to vaccines against infectious diseases, which to some extent explains the discrepancy. According to another explanation, vaccines developed against infectious diseases are considered prophylactic as they are designed to provide protection against infectious agents, while cancer vaccines have been described as therapeutic, resulting in tumor eradication and in the best-case scenario leading to a complete cure [15]. However, mRNA-based HIV vaccines have also demonstrated therapeutic activity[16]. Other explanations relate to the fact that vaccines against infectious diseases generally target large healthy populations including children with prophylactic intention. In contrast, cancer vaccines are aimed at therapeutic applications, specifically in cancer patients. However, vaccines developed against human papillomavirus, the causative agent of cervical cancer, represent an exception providing both prophylactic and therapeutic activity and has been frequently used for a vaccination strategy [17].

Another issue is the differences in the views of the FDA and the EMA. In the context of genetic manipulation and components of gene therapy, the definition of the FDA comprises the use of recombinant DNA, whereas the definition of the EMA covers the application of recombinant nucleic acids, which refers to both DNA and RNA. In this context, the focus of the FDA is on the interaction of recombinant DNA with the host DNA in the nucleus [18]. In contrast, the EMA has a broader view on recombinant nucleic acid-based drugs not only restricted to the DNA in the cell nucleus [19].

Conclusions

In summary, in a recent publication in Qeios[1] it was claimed that the clinical evaluation of mRNA-based vaccines has been insufficient, and that novel and previously unproven technologies have been used for the current COVID-19 mRNA vaccines. However, the proof-of-concept studies for mRNA-based vaccines were carried out in preclinical animal models already three decades ago. Moreover, clinical trials for mRNA-based vaccines both against infectious diseases and cancer have been conducted already at the end of the 1990s. The clinical evaluation of COVID-19 mRNA vaccines has also been described as hasty and inconclusive related to both safety and efficacy, despite the numerous approved clinical trials conducted and published in top-class peer-reviewed international journals. Hundreds of thousands of volunteers have received the COVID-19 vaccines and billions of doses have been administered in mass vaccinations in confirming the safety and efficacy of the mRNA-based COVID-19 vaccines, which has saved millions of lives and strongly contributed to the return of life to normal after global lockdowns. However, many regulatory issues related to mRNA vaccines are still unsolved and confusing related to definition of gene therapy products and vaccines, particularly related to the discrepancy in the views of the FDA, the EMA, the WHO and also issues involving manufacturing of mRNA vaccines. It is important to reach a consensus of regulatory issues to promote the processes of development, manufacturing, and approval of safer and more efficient mRNA-based vaccines.

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