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Technologies for COVID-19 and innovative therapies: contemporary challenges

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Tecnologías para la COVID-19 y terapias innovadoras: desafíos contemporáneos

Fabius Vieira Leineweber [1]
Jorge Antonio Zepeda Bermudez [2]

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[1] Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil.
[2] Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil.

Correspondence
F. V. Leineweber
Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz.
Rua Sizenando Nabuco 100, Rio de Janeiro, RJ 21041-000, Brasil.
fabius.leineweber@far.fiocruz.br

Introduction

Investments in drug or vaccine technologies to deal with the COVID-19 pandemic have consequences in the form of externalities, due to, indirect benefits in other areas related to the respective innovation [1]. The United States alone has invested more than USD 11 billion in COVID-19 medicines and vaccines (USD 3.5 billion of which in research) [2]. Global production capacity is estimated at 42 billion doses of COVID-19 vaccines in 2022, 20 billion of which originate from innovative technologies such as genetic vaccines [3]. Thus, there may be impacts on access to treatments for other comorbidities using this same range of technologies.

The recent literature has reported on the potential implications of medicines and vaccines innovations in COVID-19 for new vaccines against other infectious diseases or cancer [4]. However, the potential of these biotechnological products was already expanding before the pandemic, mainly for rare diseases. Therefore, considering a broader landscape of innovations with impacts on public health, we highlight the recent approvals related to core technologies in innovative vaccines, with a brief analysis of antibody combinations in confronting COVID-19. The article thus addresses similar technologies to innovations for COVID-19 vaccines and medicines in major regulatory agencies.

The degree of innovation for a single disease is unprecedented in the case of COVID-19. Incremental innovations may be relevant in the case of more consolidated technologies, including more traditional antibodies or vaccines. However, more innovative technologies can accelerate a biotechnological paradigm shift. Around the world, there are more than 2,300 patent applications for COVID-19 medicine and more than 100 for vaccines alone [5]. The vaccine patents are complex processes that involve licensing and disputes across various countries [6]. In addition, there are 331 treatment proposals and 260 vaccines in the pipeline [7]. The pandemic onset thus accelerates progress and repositioning of technologies with the potential to impact prices, increase opportunities, and affect regulatory processes.

Technologies for COVID-19 products

Pharmacological products for COVID-19 are classified as either treatments or vaccines. Regarding medicines, antibody development accounts for 35% of current trials. From 85 antibody therapies for COVID-19, 50 are in various clinical phases and 35 in the preclinical phase. In addition, 35 therapies are being assessed, besides another 35 antivirals. In other innovative therapies, six RNA-based treatments correspond to various mechanisms in RNA vaccines. Other treatments include devices, nanoparticles, peptides, and immunoregulators [7].

The vaccines can be included in four main categories of technologies: virus, protein, viral vector, and nucleic acid, with significant differences in their mechanisms of action and production processes [8]. The scientific effort has resulted in radical innovations in modified viral vector and messenger RNA vaccines [9].

Genetic vaccines (viral vector or nucleic acid vaccines) mimic the actual viral infection, stimulating the T-cell humoral response. Most of the viral vector vaccines use human adenovirus vectors. Since the incidence is high, the Oxford/AstraZeneca (United Kingdom) vaccine uses a chimpanzee adenovirus as the vector for stimulating the immune system [8].

Even though knowledge from similar previous products reduces current uncertainties in development, the production process, and adverse events, the speed in the development of innovative products favored their initial approvals [7].

Concerning medicines, monoclonal antibodies are also promising technologies for COVID-19. In this case, the innovations use a mixture of two or more monoclonal antibodies, a combination generated from mice and infected human cells, seeking to avoid escape due to viral mutations [10].

Similar innovative therapies and technologies for COVID-19 products

Various products have already been registered using similar technologies as vaccines developed for COVID-19. In addition to proteins and subunits, available in several medicines, nucleic acids and viral vectors are also present in some recent approvals of RNA, genetic, or cell therapies (Box 1). The degree of innovation differs in the case of gene or cell therapies, called advanced therapies by some regulatory agencies, with different approval processes [11].

Gene therapies involve treatments using genetic material. Cell therapies transfer cells, which can be autologous, heterologous, or umbilical cord stem cells; they are also called gene therapies if they are genetically modified outside the patient's body. Based on this definition, since 2003, various regulatory agencies have approved 10 products classified as gene therapies, some of which were subsequently removed from the market. Various gene therapies are currently in the pipeline, many of in clinical trials, and estimates point to 30 to 60 new products of this type by 2030 [12].

RNA therapies can also be classified as advanced therapies. They usually do not require viral vectors, but the latter may be used, as in the case of nusinersen. As shown in Box 1, nine medicines have been approved with RNA technology, seven of which with antisense RNA. Only four medicines have been approved with RNA interference technology and one drug with aptamer RNA [13].

The case of monoclonal antibodies includes incremental innovations, as products with more than one type of antibody, called polyclonal or multiclonal. The first such combination dates to 2015, and since then, many other immunotherapy regimens have been launched on the market. However, combinations for more than one target structure are recent, such as the mixture of three antibodies approved for Ebola in 2020 by the U.S. Food and Drug Administration (FDA) [14]. The production process for monoclonal antibodies is more consolidated. A study from 2018 found 34 antibodies registered in Brazil, divided into seven categories according to the activating receptors, representing an established technology [15].

Box 1

Approval, technology, and price of innovative therapies with viral vectors or RNAs.

Name	Commercial name	Medical condition	International approval	Anvisa registration	Type of therapy	Viral vector	Price
Fomivirsen	Vitravene	Cytomegalovirus infection	United States/1998 European Union/1999	2004	asRNA	-	0.8/treatment
P53 recombinant adenovirus	Gendicine	Head or neck squamous cell carcinoma	China/2003		Gene	Adenovirus	-
Pegaptanig	Macugen	Macular degeneration	United States/2004 European Union/2006	2010	Aptamer RNA	-	0.9/treatment
Cambiogenplasmid	Neovasculgen	Peripheral artery disease	Russia/2011		Gene	Plasmid	-
Sipuleucel-T	Provenge	Congenital pachyonychia	United States/2010 European Union/2013 *		Cell	-	120/treatment
Alipogene tipavorvel	Glybera	Lipoprotein lipase deficiency	EMA/2012 *		Gene	AAV1	1,000 (SD)
Mipomersen	Kynamro	Hairy cell leukemia	FDA/2013		asRNA	-	176/year
Talimogene laheparepvec	Imlygic	Multiple myeloma	FDA/2015 European Union/2015 *		Oncolytic	HSV1	65/treatment
CD34+ autologous	Strimvelis	Adenosine deaminase deficiency	EMA/2016		Gene/cell	Retrovirus	648/year
Allogenic T-Cell	Zalmoxis	Haploidentical hematopoietic stem cell transplant	European Union/2016 *		Cell	HSV	149/treatment
Nusinersen	Spinraza	Spinal muscular atrophy	United States/2016 European Union/2017	2018	asRNA	AAV9	750/1st year (340/2nd year)
Eteplirsen	Exondys 51	Duchenne muscular dystrophy	United States/2016		asRNA	-	300/year
Tonogenchocle-L	Invossa	Osteoarthritis	South Korea/2017 *		Gene/cell	Retrovirus	-
Voretigen neparvovec	Luxturna	Retinitis pigmentosa/ Leber congenital amaurosis	United States/2017 European Union/2019	2020	Gene	AAV2	425/eye (SD)

(continues)

Box 1 (continued)

Name	Commercial name	Medical condition	International approval	Anvisa registration	Type of therapy	Viral vector	Price
Axicabtagen ciloleucel	Yescarta	Diffuse large B-cell lymphoma	United States/2017 European Union/2018		Gene/cell	Retrovirus	373/treatment
Tisagenleuclecel	Kymriah	Acute lymphoblastic leukemia	United States/2018 European Union/2018		Cell	Lentivirus	475/treatment
Inotersen	Tegsedi	Hereditary transthyretin amyloidosis	United States/2018 European Union/2018	2019	asRNA	-	450/year
Patisiran	Onpattro	Hereditary transthyretin amyloidosis	United States/2018 European Union/2018	2019	RNAi	-	450/year
Betibeglogene autotemcel	Zynteglo	Beta thalassemia	United States/2019		Gene/cell	Lentivirus	1,800 (SD)
Onasemnogene abeparvovec	Zolgensma	Spinal muscular atrophy	United States/2019 European Union/2020	2020	Gene	AAV9	2,000 (SD)
Givosiran	Givlaari	Acute hepatic porphyry	United States/2019 European Union/2020		RNAi	-	575/year
Golodirsen	Vyondys 53	Duchenne muscular dystrophy	United States/2019		asRNA	-	300/year
Brexucatagene autoleucel	Tecartus	Mantle cell lymphoma	European Union/2020		Gene/cell	Retrovirus	373/year
Lumasiran	Oxlumo	Type-1 primary hyperoxaluria	United States/2020 European Union/2020		RNAi	-	493/year
Viltolarsen	Viltepso	Duchenne muscular dystrophy	United States/2020		asRNA	-	733/year
Inclisiran	Leqvio	Hairy cell leukemia	United States/2020		RNAi	-	-

AAV: adeno-associated virus; Anvisa: Brazilian Health Regulatory Agency; asRNA: antisense RNA; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; HSV: herpes simplex virus; RNAi: RNA interference; SD: single dose.

Source: prepared by the authors using data from regulatory agencies (FDA, EMA, Anvisa) and prices from Google search (United States): commercial name + price.

Note: excludes umbilical cord stem cell therapies.

* Withdrawn from market.

Challenges

These production processes and technologies related to advanced therapies bear similarities to vaccines under development for COVID-19. The processes share many inputs and operational production equipment.

The vehicles for advanced therapies present significant scientific externalities. RNA, lipid nanoparticles, polymers, or conjugates can offer therapeutic advantages for other drug classes. Meanwhile, adenoviruses are more commonly used for cancer vaccines and therapies, due to the immunogenic response, besides the shorter duration and higher expression [16]. Before the enormous progress against COVID-19, there were no widely registered vaccines with adenoviruses (only one Russian vaccine for emergency use and a Chinese cancer vaccine) [17].

Subsequently, the knowledge of mechanisms of action represents a major improvement. Advanced therapies are frequently applied to rare diseases, due both to the regulatory incentive and as preferential targets for genetic point mutations, more easily determined than in the case of complex diseases that involve multiple genes [11]. Hence, although advanced therapies currently compete with vaccines for materials and production capacity, the long-term technological horizon points to potential progress for both.

The main challenge involves the high prices of advanced therapies. Estimates for the development of new medicines exceed billions of dollars, based on industry data [18]. In the case of rare diseases, the recovery of this investment occurs in a very small number of patients, and the initial registrations are limited to high-income countries. Although scaling up and improvements in production technology can help reduce costs, cooperation and solidarity in access are essential for more equitable and fair prices for countries.

Analogously, monoclonal antibodies can also benefit from the global production scale, reducing costs and allowing recovery of Research & Development investments with more favorable prices, with the expansion of access in the world, including governments in peripheral countries that could serve their population with lower budget expenditures.

In Brazil, recent approvals by the National Committee for Health Technology Incorporation (CONITEC) for nusinersen, with expanded use, result in a budget impact of more than BRL 2 billion (USD 400 million) by 2025 [19]. Although Health Technology Horizon Scanning reveals few advanced therapies [20], we observe a much broader range of medicines in this scope recently approved in the international setting. Accordingly, the relations between vaccine technologies with expanded production capacity and access allow forecasting this supply acceleration in the coming years.

Most innovations (Box 1) are for treatments of rare diseases. Brazil's National Policy on Comprehensive Care for Persons with Rare Diseases initially implemented 15 molecular biology and cytogenetic tests and immunoassays, besides genetic counseling and three diagnostic procedures. In Brazil, there are currently 36 Standard Treatment Guidelines for Rare Diseases [21]. However, 90% of lawsuits involve orphan diseases, and the number of Brazilians diagnosed with rare diseases increased 150% in the last four decades [22]. In 2018, the Brazilian Federal Government spent BRL 1 billion (USD 200 million) on medicines obtained by patients through lawsuits. If we add states and municipalities, the total reaches BRL 7 billion (USD 1.4 billion) a year [23]. Due to knowledge gaps on this topic, research agencies have recently issued calls for projects to research rare genetic diseases and innovative platforms in advanced therapies [24].

Although the scope of this article is the possible influence of vaccines and some treatments, technologies used for COVID-19 in public health are not limited to this. The increase of testing capacities, apps for notifying exposure, and user-friendly contact-tracing technologies would be epidemiologically relevant for orienting health system needs, especially for infectious diseases.

Final remarks

The opportunities for global cooperation are similar for COVID-19 therapies and vaccines and innovative therapies for personalized medicine. However, the increase in health expenditures worldwide may exceed the payment capacity of individuals, insurance companies, and health systems. The possible affordability on various countries would mitigate restrictions in access, as discussed in forums of the United Nations agencies and included in the *Sustainable Development Goals*.

The pandemic has highlighted the divergence between solidarity to ensure the right to universal health and market competition. The competition for health products is not an isolated issue from prevailing geopolitical and economic arrangements. The sustainability of increasingly personalized treatments challenges healthcare supply and demand in countries with universal systems. In Brazil, this share of the population benefited by these advanced therapies tends to grow, and a better response to the scenario by the Brazilian Unified National Health System (SUS) involves adequate financing and multilateral cooperation to allow scientific progress accesses for the population.

Contributors

F. V. Leineweber contributed to the search for references, data collection and preparation of the text. J. A. Z. Bermudez contributed to the writing and revision of the text.

Additional informations

ORCID: Fabius Vieira Leineweber (0000-0003-4151-449X); Jorge Antonio Zepeda Bermudez (0000-0002-4657-0709).

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