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Commentary

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Future Drug Discovery

Breakthrough medicines during the COVID-19 pandemic era

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"In the midst of the pandemic, there were about 5587 (2020) and 4810 (2021) approvals granted by FDA for number of indications."

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The COVID-19 pandemic has presented an unprecedented challenge by imposing a dramatic loss to human life worldwide. It has had devastating effects on social and economic status [1]. COVID-19 was caused by a zoonotic virus, namely novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) [2]. Globally, as of 23 December 2021, more than 5.3 million deaths were reported to the WHO. The COVID-19 pandemic has not yet ended, and because of constant viral mutations it poses a challenge to the medical community. Recently there have been major breakthroughs in developing mRNA vaccines, monoclonal antibodies, and various other therapeutic agents for COVID-19 [3].

Besides the pandemic, it was also focused towards medical and research innovation efforts in the context of development of vaccines, medications, diagnostic/prognostic predictors and biomarkers, screening, transplantation, testing and point-of-care kits, wearable technologies, artificial intelligence, etc. During the last 2 years, notable and unprecedented research resulting in major breakthroughs includes artificial intelligence models for improving cancer and autism detection, discovering cellular mechanisms on genetic mutations in amyotrophic lateral sclerosis, genomic-based targeted and genetic-inhibited cancer treatment, cancer cell hijack mechanisms, immunotherapies, CAR-T therapies, and so on. The pandemic has not slowed the discoveries that led to unprecedented research resulting in major breakthroughs in various human diseases. In this commentary article, we present the most impactful breakthrough medicine innovations for tackling COVID-19, Ebola virus disease (EVD), heart diseases, cancer, Alzheimer's disease, diabetes, and malaria during the pandemic period that have a profound meaning and positive impact on human lives.

Breakthrough medicines

Many therapeutic agents or drug molecules are available in the market to protect mankind from dreadful diseases. However, a diverse array of adverse effects are brought into account with drug usage at therapeutic or non therapeutic doses [4]. There is a need to consider the benefit-risk balance. Drug safety has earned a lot of attention as it plays a pivotal role in the development of various medical therapies and novel treatments. Drugs with a high-risk profile should be avoided unless there is an emergency use. Pregnant and lactating women, children and old people are considered as vulnerable groups and appropriate precautions need to be taken before administering medications for these groups [5]. In children, it is very important to use the recommended dose to avoid side effects. Protection of public health by ensuring the efficacy, safety, and security of human drugs is inevitable. The US FDA is taking this

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responsibility as a key component [6]. In the midst of the pandemic, there were about 5587 (2020) and 4810 (2021) approvals granted by FDA for number of indications. These approvals included as approved supplements, tentative approvals, orphan drugs, emergency use authorization (EUA), and full approvals. In this article, we have mentioned a brief outline of the most important and novel breakthrough medicines during the COVID-19 pandemic. This article also explains the composition and mechanism of action of these FDA approved breakthrough medicines against intended diseases.

Coronavirus disease

COVID-19, an infectious disease caused by the SARS-CoV-2 virus, is a serious problem, responsible for the current pandemic with extensive morbidity and mortality throughout the world. SARS-CoV-2 uses the same receptor as SARS-CoV, ACE2 [7]. The COVID-19 vaccine drive has made marked progress in minimizing hospitalizations and deaths. RNA and DNA vaccines used genetically engineered RNA or DNA that encode a protein, which provides prompt immune response [8]. According to the 'Our World in Data' report, as of 23 December 2021, about 61% of the US population is fully vaccinated in addition to about 11% of the US population that is partially vaccinated against COVID-19 disease [9]. The FDA approved COVID-19 vaccines (Pfizer-BioNTech, Moderna, and Johnson & Johnson) protect patients against severe illness and hospitalizations due to COVID-19 disease. Pfizer-BioNTech COVID-19 vaccine has an active ingredient, nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. On 23 August 2021, the FDA approved the Pfizer-BioNTech COVID-19 vaccine after initial EUA in December 2020. The Moderna COVID-19 vaccine is composed of nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 as an active ingredient [10]. Both the Pfizer and Moderna vaccines provide a blueprint for the cells by using mRNA, and buildup the body's defense against the virus by allowing the generation of an antibody response which can attack the virus if the vaccinated individual is exposed. Johnson & Johnson's COVID-19 vaccine contains recombinant replication-incompetent adenovirus type 26 vector, that encodes a stabilized variant of the SARS-CoV-2 spike (S) protein as an active ingredient. It triggers an immune response and mimics natural infection; thereby, protecting people against future infections [11]. The FDA approved the first antiviral oral drugs, Paxlovid™ (ritonavir, Pfizer) and Lagevrio Lagevrio (molnupiravir, Merck & Co) for the treatment of mild-to-moderate COVID-19 adults and pediatric patients under an EUA. These drug molecules act as polymerase inhibitors and work against replication of the virus genetic material. In addition, Veklury® (remdesivir, Gilead), an intravenous infusion medication of SARS-CoV-2 nucleotide analog RNA polymerase inhibitor chemically named as 2-ethylbutyl N-{(S)-[2-C-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-Oyl]phenoxyphosphoryl}-L-alaninate, has been authorized under EUA for COVID-19 treatment. Besides, some drugs and non vaccine biological products, like Evusheld™ (tixagevimab copackaged with cilgavimab, AstraZeneca), Actemra® (tocilizumab, an IL-6 receptor antagonist, Genentech), Xevudy™ (sotrovimab, GlaxoSmithKline plc and Vir Biotechnology, Inc.), bamlanivimab and etesevimab together (for post exposure prophylaxis in subjects who meet high-risk criteria, Lilly), REGEN-COV (casirivimab and imdevimab, Regeneron Pharmaceuticals), and baricitinib (Olumiant, Lilly) were also permitted to use under EUAs.

EVD

EVD is a viral hemorrhagic fever disease that can be transmitted through direct contact with a deceased person or a sick person infected with the Ebola virus, or with an infected animal. EVD is a potentially fatal disease in humans. Inmazeb™ (Regeneron Pharmaceuticals Inc.), a mixture of three monoclonal antibodies, namely maftivimab, atoltivimab, and odesivimab-ebgn, is the first FDA approved drug to treat Zaire ebolavirus (EBOV) infection in pediatric and adult patients [12]. This triple antibody combination efficiently neutralizes the virus by blocking the virus entry into host cells. Similarly, Ebanga (Ansuvimab-zykl), is a single-dose intravenous recombinant human IgG1k monoclonal antibody used to treat EBOV infection in children and adults. It prevents the virus from entering into the cells by binding the virus to the glycoprotein 1 subunit of EBOV, preventing the binding of EBOV to host cells.

Heart diseases

Cardiovascular disease produces immense health and economic burdens. Ischemic heart disease, the leading cause of death in the world, is responsible for 16% of the world's total deaths, whereas stroke is the second leading cause of death that is responsible for approximately 11% of total deaths. Hypertension, cardiovascular disease, diabetes mellitus, and severe obesity are the main risk factors for heart disease with varying impacts depending on the age

of the individual and the country of origin [13]. In 2021, FDA approved the usage of Kerendia® (finerenone, non steroid mineralocorticoid receptor agonist, Bayer) for the reduction of heart attacks, hospitalization for heart failure and cardiovascular deaths for adults with chronic kidney disease associated with Type 2 diabetes [14]. This drug is demonstrated to be helpful in people with Type 2 diabetes at various stages of kidney disease to improve their heart health. On 20 January 2021, Merck announced that Verquvo® (vericiguat), a soluble guanylate cyclase (sGC) stimulator, is approved to mitigate the risk of cardiovascular death and hospitalization by chronic heart failure. Nexletol® (bempedoic acid), is a newly approved drug that efficiently reduces cholesterol synthesis via inhibition of adenosine triphosphate citrate lyase (an enzyme upstream from 3-hydroxy-3-methylglutaryl-coenzyme A). This prescription is being used along with a proper diet and other medications to help lower 'bad' cholesterol in the blood (reducing the amount of cholesterol made by the liver), ultimately minimizing the risk of heart disease and lowering the incidence of strokes and heart attacks.

Cancer

Cancer is a major public health problem worldwide and is the second leading cause of death in the US. According to the American Cancer Society, there are about 1,898,160 new cancer cases diagnosed and approximately 608,570 people died from cancer in the US in 2021 [15]. A large number of agents, antibodies and drug-conjugates are being developed for the treatment of various cancers. For example, Cytalux™ (Target Laboratories, Inc.), a fluorescent drug that targets folate receptors, is a new FDA approved drug that is composed of pafolacianine and is used to identify ovarian cancer lesions during surgery in adult patients. On 29 October 2021, Scemblix® (asciminib, Novartis), a kinase inhibitor, was approved to treat Philadelphia chromosome-positive chronic myeloid leukemia. Asciminib has a distinct mechanism of action that binds to the BCR-ABL1 Myristoyl Pocket. Thus, it helps to address resistance in patients with chronic myeloid leukemia (CML) previously treated with two or more tyrosine kinase inhibitors (TKIs) and overcome mutations at the defective *BCR-ABL1* gene. Besides, other kinase inhibitors such as Retevmo® (selpercatinib, Eli Lilly and Company) and Tabrecta® (capmatinib, Novartis) are approved to treat lung, thyroid, and non-small cell lung cancer (NSCLC), respectively.

Tivdak™ (tisotumab vedotin-tftv, Seagen), is a microtubule inhibitor conjugate and a tissue factor-directed antibody, indicated to treat recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Likewise, Exkivity™ (mobocertinib, Takeda), a kinase inhibitor, was approved on 15 September 2021, for the treatment of metastatic or locally advanced NSCLC. This drug is effective in patients with EGFR exon 20 insertion mutations and whose disease has progressed on or after platinum-based chemotherapy. Rylaze™ (asparaginase erwinia chrysanthemi (recombinant)-rywn, Jazz Pharmaceuticals Ireland Limited), an asparagine-specific enzyme, used to treat lymphoblastic lymphoma and acute lymphoblastic leukemia in *E. coli* derived asparaginase products-allergic patients. Lumakras™ (sotorasib), an inhibitor of the RAS GTPase family (KRAS G12C inhibitor), is indicated for the treatment of various types of NSCLC (*KRAS* G12C positive) are locally advanced or metastatic and who have received at least one prior treatment. Pylarify® (piflufolastat F 18 or 8F-DCFPyL or PyL, Progenics Pharmaceuticals, Inc.), a radioactive diagnostic agent, approved to recognize prostate-specific membrane antigen (PSMA) positive lesions in prostate cancer. Rybrevant® (amivantamab-vmjw, Janssen Biotech, Inc.), a bispecific EGFR antibody treatment, is recommended to treat a subset of NSCLC (EGFR exon 20 insertion mutations). Under accelerated approval, Zynlonta (loncastuximab tesirine-lpyl, ADC Therapeutics SA), an alkylating agent conjugate and CD19-directed antibody, meant to treat various types of refractory or relapsed large B-cell lymphomas. In addition, Jemperli (dostarlimab-gxly, GlaxoSmithKline), a programmed cell death receptor-1 (PD-1) blocking antibody, approved for the treatment of adult patients with mismatch repair-deficient (dMMR) recurrent or advanced solid tumors. While, Fotivda® (tivozanib, an oral VEGF receptor tyrosine kinase inhibitor, AVEO Pharmaceuticals, Inc.) and Tepmetko® (tepotinib, Merck KGaA) are the kinase inhibitors that were approved to treat endometrial cancer, refractory or relapsed advance renal cell carcinoma and NSCLC, respectively. Other kinase inhibitors like Cosela™ (trilacicilib, G1 Therapeutics, Inc.) and Ukoniq® (umbralisib, TG Therapeutics Inc.) are used to reduce the chemotherapy-induced myelosuppression in small cell lung cancer, and treat follicular lymphoma and marginal zone lymphoma respectively. Similarly, Tukysa® (tucatinib, Seagen Inc.) and Ayvakit™ (avapritinib, Blueprint Medicines Corporation), also a kinase inhibitor, have been clinically used for the treatment of advanced unresectable or metastatic HER2-positive breast cancer in combination with trastuzumab and capecitabine, and metastatic gastrointestinal stromal tumors.

In 2020, the FDA approved Orgovyx™ (relugolix, androgen deprivation therapy, Myovant Sciences GmbH and Pfizer Inc.), a gonadotropin-releasing hormone (GnRH) receptor antagonist, which is indicated for the treatment

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of advanced prostate cancer. In addition, Margenza® (margetuximab [anti-HER2 mAb], MacroGenics, Inc.), a HER2/neu receptor antagonist, in combination with chemotherapy, is used to treat HER2+ breast cancer. Similarly, Gallium 68 PSMA-11 (Gallium 68 PSMA-11), a radioactive diagnostic agent, is indicated to identify the positive lesions of PSMA in men using positron emission tomography (PET). Gavreto® (pralsetinib, Blueprint Medicines Corporation and Genentech, Inc.), a kinase inhibitor, is used to treat NSCLC. Monjuvi® (tafasitamab-cxix, MorphoSys AG), a CD19-directed cytolytic antibody, in combination with lenalidomide, is used for the treatment of relapsed or refractory diffuse large B-cell lymphoma. Zepzelca™ (lurbinectedin, Jazz Pharmaceuticals), an alkylating drug, is indicated to treat metastatic small cell lung cancer. In May 2020, Cerianna™ (fluoroestradiol F18, Zionexa USA), a radioactive diagnostic agent, is used for the detection of estrogen receptor (ER)-positive lesions with PET in patients with metastatic breast cancer. Trodelvy™ (sacituzumab govitecan-hziy, Gilead Sciences, Inc.), a Trop-2-directed antibody and topoisomerase inhibitor conjugate, is used to treat adult patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease.

Alzheimer's disease

An estimated 6.2 million Americans (≥65 years) are surviving with Alzheimer's dementia in 2021 [16]. Women are inordinately affected and, in 2019, it was ranked as the 7th leading cause of death. FDA approved the drugs such as Aduhelm® (aducanumab-avwa, Biogen)- an amyloid beta-directed antibody (approved in 2021) and Tauvid™ (flortaucipir F18, Eli Lilly and Company) a radioactive diagnostic agent (approved in 2020) for the treatment and diagnostic purposes.

Diabetes

Diabetes, a chronic disease characterized by elevated levels of blood glucose, has entered the top ten leading causes of death. It is also responsible for the largest rise in deaths in males among the top ten, with an 80% increase, since 2000. In 2021, Kerendia (Bayer), a non steroidal mineralocorticoid receptor antagonist, is a drug approved for the usage by FDA to reduce the risk of heart and kidney complications associated with Type 2 diabetes. It is composed of finerenone [17].

Malaria

Human malaria is one of the most rampant human infectious diseases worldwide [18]. As per the Centers for Disease Control and Prevention, approximately 2000 cases of malaria were being diagnosed in the US each year. Patients often experience fever, flu-like illness, chills and chronic conditions that may cause severe complications like seizures, kidney failure, mental confusion and death. Artesunate (Amivas US, LLC) is the first-line treatment for children or adults with severe malaria, in combination with other antiviral agents.

In addition to the above notable breakthrough medicines, NTLA-2001 (Intellia Therapeutics), an Investigational CRISPR therapy to treat transthyretin amyloidosis, acts by editing targeted human TTR gene [19]. Zokinvy (lonafarnib, Eiger BioPharmaceuticals) is an orally active farnesyltransferase inhibitor used to prevent premature aging and to treat progeroid and progeria laminopathies [20]. A triterpenoid antifungal, Brexafemme® (ibrexafungerp, Scynexis, Inc.), is used for the treatment of post menarchal pediatric females and adults with vulvovaginal candidiasis [21].

Conclusion

The past 2 years, marked as the COVID-19 pandemic era, posed an unprecedented challenge to all human beings across the globe. The innovations and hard work of pharmaceutical and medical sciences in 2020 and 2021 resulted in many therapeutic lead molecules making to the list of FDA approvals. This includes several small molecules, monoclonal antibodies, imaging agents and antibody-drug conjugates for numerous unmet clinical needs. Together, the efforts of this commentary article are to provide some novel breakthrough medicines that are evident for successful clinical use for coronavirus disease, EVD, heart disease, cancer, Alzheimer's disease, diabetes and malaria. However, some emergency authorized use recommendations have to be analyzed further for their long-term clinical safety and continued usage.

Author contributions

ENHK Ghali and MM Yallapu conceived the idea and wrote the major portion of the manuscript and editing. The manuscript was also written and edited by V Dhevan, SK Narmala, M Jaggi, and SC Chauhan. The final manuscript has been read and approved by all authors.

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