EDITORIAL

Drugs in Context Editorial: Review of 2020 and what lies ahead in therapeutic interventions

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Abstract

The year 2020 was dominated by the COVID-19 pandemic, bringing with it unprecedented advancements in the fields of healthcare and therapeutic interventions as well as in vaccine and drug development. Nevertheless, several other advancements in various fields of medicine also deserve attention. Herein, the Senior Editors of Drugs in Context provide us with their expert opinion on the events of 2020 and what lies ahead in 2021.

Keywords: antimicrobial resistance, beta-lactams, COVID-19, dexamethasone, insulin icodect, SGLT2 inhibitors, statin therapy, type 2 diabetes.

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Sarah L Anderson

As the year 2020 came to a close, I was struck by the numerous advancements in pharmacotherapy related to the COVID-19 pandemic. Remdesivir, an antiviral agent approved for the treatment of patients with COVID-19 (aged 12 and over and who weigh at least 40 kg) requiring hospitalization, received conditional marketing authorization in the European Union on July 3, 2020. In the United States, remdesivir was granted Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) on May 1, 2020, and then full FDA approval on October 22, 2020.¹,² On November 9, 2020, the FDA issued an EUA for bamlanivimab, a monoclonal antibody therapy for the treatment of mild-to-moderate COVID-19 in patients aged 12 and over who weigh at least 40 kg who have a positive SARS-CoV-2 test and who are at high risk for progression to severe COVID-19 and/or hospitalization.³ Most recently, the United Kingdom, Canada and the United States granted approval of the Pfizer-BioNTech COVID-19 vaccine to be used under emergency use conditions. The European Medicines Agency (EMA) reviewed the vaccine on December 21, 2020, and also recommended marketing authorization.⁴ The speed at which these COVID-19 treatments and vaccines were studied and approved for use was unprecedented but necessary given the escalation of the pandemic. The approval of the COVID-19 vaccine represents a hopeful beginning of the end of the COVID-19 pandemic.

In addition to the COVID-19-related drug therapy and vaccine approvals, there were many other important drug therapy advances in the cardiometabolic realm that should not be overlooked. The year 2020 saw a multitude of data published regarding the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with and without diabetes. Notably, the EMPEROR-Reduced trial added to the growing body of evidence that SGLT2 inhibitors have beneficial cardiovascular effects in patients with heart failure with reduced ejection fraction (HFrEF), both with and without diabetes.⁵ A sub-analysis of the 2019 study DAPA-HF, in which patients with and without diabetes with HFrEF were treated with dapagliflozin, demonstrated a 32% reduction in the relative risk of incident type 2 diabetes (T2D) in patients who did not have T2D at the start of the trial.⁶,⁷ Lastly, data continues to emerge regarding the use of SGLT2 inhibitors for type 1 diabetes (T1D). The DEPICT-1 and DEPICT-2 trials demonstrated that dapagliflozin was effective at reducing both haemoglobin A1C and weight with no increase in hypoglycaemia in patients with T1D.⁸ This adds to the existing data of sotagliflozin and low-dose empagliflozin demonstrating glycaemic control and other benefits in patients with T1D.
Other notable advances in cardiometabolic drug therapy in 2020 include the new drug approval of bempedoic acid for cholesterol lowering in patients intolerant to statins and the new indication of recurrent stroke prevention for ticagrelor. Bempedoic acid, an adenosine triphosphate–citrate lyase inhibitor, was approved by the EMA on January 31, 2020, and by the FDA on February 24, 2020, as an adjunct to maximally tolerated statin therapy in patients with established atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolaemia. Bempedoic acid exhibits little to no propensity for causing myalgias, which will likely influence its role in therapy as described in future cholesterol guidelines.9 Data from the THALES trial led to the expanded indication of ticagrelor for the prevention of recurrent stroke. The THALES trial demonstrated that, in patients with acute ischaemic stroke or transient ischaemic attack, ticagrelor 90 mg orally daily plus aspirin significantly reduced the rate of composite stroke and death compared to aspirin monotherapy.10

As we look forward to 2021, items of interest include the anticipation of data regarding COVID-19 vaccine durability – it is currently unknown how many months of efficacy and protection the vaccine provides. Outside of COVID-19 therapeutics, the recent approval of inclisiran, a small interfering RNA, by the EMA for use in combination with maximally tolerated statin therapy in patients unable to achieve lipid targets, will influence how we treat hypercholesterolaemia.11 The development of a once-weekly basal insulin injection (insulin icodec) for patients with T2D is also of great interest for clinicians who care for patients with T2D as this could revolutionize insulin therapy and insulin adherence.12 We will undoubtedly continue to see emerging data related to COVID-19 therapeutics but I anticipate that progress with therapeutics in the cardiometabolic realm will also continue to advance.

Matteo Bassetti

Without any doubt, the infectious diseases scenario in 2020 has been dominated by the COVID-19 pandemic. Besides the unfortunately large diffusion of the virus and the related overwhelming burden in terms of morbidity and mortality worldwide, the indirect effects of the pandemic on the societal and economic levels are also of major concern, putting some highly affected areas at risk of unacceptable increases in poverty and unemployment.13,14 On the positive side, the pandemic has highlighted the resilience of science and impressive collaborative efforts around the world have allowed an unprecedented speed in achieving pivotal research milestones. Among others, (i) the genome of SARS-CoV-2 was rapidly sequenced and shared publicly upon diffusion of the virus in China;15 (ii) randomized controlled trials have been conducted in record time and have provided high-level evidence for guiding (or discouraging) different treatments within months from SARS-CoV-2 appearance;16 and (iii) the development of vaccines has been advanced up to completing rigorous, large phase III randomized trials in less than 1 year and vaccination campaigns have already started in several countries.17 In summary, there is much hope that a great reduction in the heavy burden posed by COVID-19 on humankind will be observed within 2021. Should this hope be confirmed, this last year may have provided a crucial lesson that must be extrapolated to contexts other than COVID-19, for example, to antimicrobial resistance. In this regard, several novel antibiotics active against difficult-to-treat Gram-negative bacteria have recently obtained approval by the FDA and the EMA.18 The quest for an optimal treatment of infections caused by such perilous organisms has been very long (and, in part, is still ongoing). For example, it has taken several years to renew the availability of beta-lactams or beta-lactam/beta-lactamase inhibitor combinations active against carbapenem-resistant Gram-negative bacteria.19 This is no longer acceptable and the great collaborative efforts made for COVID-19 research should pave the way to similar concerted efforts to better and more rapidly tackle antimicrobial resistance. We should do this now more than ever, since the disruptive effects of COVID-19 also touched on established infection control and antimicrobial stewardship initiatives aimed at reducing the spread of resistant bacteria.20 When it comes to antimicrobial resistance in the COVID-19 era, we may have taken a perilous step backward — we now need to take a giant step forward.

Arduino A Mangoni

Whilst 2020 was primarily characterized by the conduct of studies investigating the effects of anti-viral and immunomodulatory strategies in patients with COVID-19, significant advances have also been made in the management of several chronic disease states, including cardiovascular disease, chronic kidney disease and diabetes. Despite the early identification of the mechanisms involved in the transmission and pathogenesis of SARS-CoV-2, intervention studies have failed to demonstrate the tangible effects of repurposed antiviral agents, i.e. hydroxychloroquine, remdesivir, lopinavir and interferon-β1a, on clinical outcomes in patients with COVID-19.21–23 Concerningly, these studies have largely excluded older patients with different degrees of co-morbidity, polypharmacy and frailty — the group with the highest risk of infection and adverse outcomes.24 The only agent that has shown significant beneficial effects in COVID-19, the corticosteroid dexamethasone, acts primarily by suppressing the excessive inflammatory response in the lung and other organs, namely the cytokine storm, in patients with the more severe forms of the disease.25 Notably, in the landmark study of dexamethasone by the RECOVERY collaborative group, 15–22% of participants were aged 70–79 years and 2–35% were aged ≥80 years across the different treatment arms. The relatively high prevalence of common disease states in old age in this study, particularly diabetes (22–25%), heart disease (16–34%) and lung disease (11–23%), further facilitates the generalizability of the findings.26 Pending the development and the distribution of safe and effective vaccines, further efforts are...
expected in the identification of pharmacological treatments to suppress viral replication and/or prevent the significant alterations in immune response and coagulation observed in COVID-19. The study of combinations of available agents, targeting different pathophysiological pathways, might also lead to better management strategies. In this context, machine learning, a subset of artificial intelligence, might assist with the identification of patient characteristics or patient groups that are associated with better outcomes with specific treatments, thereby playing a key role in the design of further intervention trials.

The therapeutic applications of SGLT2 inhibitors, a relatively new class of oral antidiabetic agents, are likely to expand following the results of two randomized controlled trials. In 4,304 patients with chronic kidney disease, with or without T2D, dapagliflozin treatment was associated with a significant reduction in the primary outcome, a composite of decline (≥50%) in glomerular filtration rate, end-stage renal disease, or death from renal or cardiovascular causes versus placebo (HR 0.61, 95% CI 0.51–0.72; P<0.001). In 3,730 patients with heart failure and an ejection fraction ≤40%, empagliflozin treatment was associated with a significant reduction in the primary outcome, namely a composite of cardiovascular death or hospitalization for worsening heart failure, when compared to placebo (HR 0.75, 95% CI 0.65–0.86; P<0.001). The effect was consistent regardless of the presence of diabetes.

The described reno-protective and cardio-protective effects of SGLT2 inhibitors, albeit promising, require additional confirmatory studies in different patient populations. Experimental and human studies are also needed to identify the mechanisms responsible for the observed beneficial effects of this class of drugs. In patients with T2D and chronic kidney disease, an additional therapeutic option is likely represented by the non-steroidal selective mineralocorticoid receptor antagonist finerenone. In a study of 5,734 patients with T2D, microalbuminuria, chronic kidney disease and diabetic retinopathy, treatment with finerenone was associated with a significant reduction in kidney failure or death from renal causes (HR 0.82, 95% CI 0.73–0.93; P=0.001). Further insights into the effects of finerenone in patients with T2D and milder degrees of chronic kidney disease are expected after the completion of another study, the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-CKD) trial.

In the field of heart failure, important developments have occurred with regard to a novel class of inotropes, the cardiac myosin activators. Omecamtiv mecarbil, the first agent of this class, significantly reduced, albeit modestly, a first heart failure event or cardiovascular death versus placebo in 8,256 patients with HFREF (HR 0.92, 95% CI 0.86–0.99; P=0.03). The promising role of myosin as a drug target in cardiovascular disorders is further supported by the recent evidence of efficacy with mavacamten, a cardiac myosin ATPase inhibitor that reduces cardiac contractility, improving myocardial energetics.

In 251 patients with hypertrophic cardiomyopathy, treatment with mavacamten was more likely to be associated with a significant improvement in peak oxygen consumption, with or without symptoms of heart failure, versus placebo (difference +19.5%, 95% CI 8.7–30.1; P=0.005).

Another study published in 2020 is likely to influence the management of atrial fibrillation, a common arrhythmia in the older population. In this group, clinicians often face the challenges of balancing the therapeutic effects of anticoagulant treatment, i.e. stroke prevention, with the inherent risk of bleeding. A possible strategy in this group is the use of lower than recommended doses of anticoagulants to achieve a more favourable risk-to-benefit ratio. A total of 984 Japanese patients aged ≥80 years with non-valvular atrial fibrillation were randomized to placebo or edoxaban 15 mg daily. The usual recommended dose of edoxaban, a direct oral anticoagulant, is 60 mg daily (30 mg daily in the presence of renal impairment). When compared to placebo, low-dose edoxaban treatment was associated with a significant reduction in the risk of stroke and systemic embolism (HR 0.34, 95% CI 0.19–0.61; P<0.001) and a non-significant increase in the risk of major bleeding (HR 1.87, 95% CI 0.90–3.89; P=0.09). Pending further studies in different ethnic groups, low-dose anticoagulant treatment might represent a safe and effective strategy for the management of atrial fibrillation in the older patient. A modification in the administration of available therapies might also be useful in other disease states, for example, diabetes. A reduced frequency of basal insulin injections, from once daily to once weekly, might further enhance treatment adherence. In a phase II study of 247 subjects with T2D, treatment with insulin icodextr, a recently developed once-weekly insulin, caused similar reductions in glycaemic control and the micro-vascular and macro-vascular complications in patients with T2D.

Significant developments have also been made in the search for effective treatment strategies to reduce cardiovascular risk by targeting the excessive inflammatory burden observed in atherosclerosis. In 5,522 patients with chronic coronary disease, treatment with the marketed anti-inflammatory drug colchicine significantly reduced a composite endpoint of cardiovascular death, myocardial infarction, ischaemic stroke or coronary revascularization when compared to placebo (HR 0.69, 95% CI 0.57–0.83; P<0.001). Pending additional studies, the repurposing of colchicine for cardiovascular prevention might represent a safe and relatively inexpensive strategy with significant public health benefits, given the global burden of atherosclerotic cardiovascular disease.

In 2021, further pharmacotherapeutic advances are likely to occur in the cardiovascular field, particularly regarding the potential use of SGLT2 inhibitors in atherosclerotic cardiovascular disease and the repurposing of available anti-inflammatory drugs other than colchicine for cardiovascular risk management.
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