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Compassionate drug use: an imperative challenge for Bulgarian health system during COVID-19

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During the past few months, the global community faces significant challenges, trying to take control over the pandemic of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 COVID-19). According to data provided by Johns Hopkins University (update for April 27, 2020), COVID-19 has spread to 199 countries and infected 2,898,703 people globally, leading to 203,043 deaths (7.00% case-fatality ratio). The respective statistics for the same date in Bulgaria, indicate 1,247 infections and 55 deaths (4.26% case-fatality ratio), accounting for 0.04% of global infections and 0.03% of total deaths [1].

Similar to other European countries, the Bulgarian government rapidly implemented a series of comprehensive and preventive control measures to tackle the pandemic [2]. Despite several clinical trials are currently in place, there are still no specific therapies or any vaccine against COVID-19, approved by the Food and Drug Administration (FDA), European medicines Agency (EMA), as well as the Bulgarian Drug Agency (BDA) [3]. The only option available is using off-label or compassionate use (CU) therapies, including antiviral agents, antiparasitic agents, anti-inflammatory compounds, and convalescent plasma [4]. As the SARS-CoV-2 continues to spread rapidly across the world, the request numbers for CU has risen exponentially.

As all the health care systems, the Bulgarian faces unprecedented challenges and health policymakers are under pressure to implement quick reforms and effective measures during pandemic. The main characteristics of the Bulgarian health care system, including a high level of centralization, a single payer to administer social health insurance, as well as limited supply of workforce and bed capacity of intensive care units (ICU). Bulgaria recently introduced a Health Technology Assessment (HTA) framework which relies on clinical and economic criteria and adopted particular steps for pricing and reimbursement of new medicines [5]. The global pandemic mandates BDA for reasonable update of the existing national regulation and procedures concerning CU and off-label therapies. In era of the COVID-19 era, it is essential for Bulgarian patients to have early and expanded access to investigational drugs for compassionate therapies. CU, also referred to as expanded access, is the therapeutic use of investigational drugs outside of clinical trials. EMA defines as CU a treatment option that allows the use of an unauthorized medicinal product which is under development [3].

The clinical and ethical significance of the CU finds its basis in the Declaration of Helsinki - ART.37. Seventeen out of the 27 EU member states have well-defined national regulations and procedures for the CU of drugs [6].

In EU and Bulgaria as well, the legal framework for CU was introduced by Article 83 (1) of Regulation (EC) No 726/2004 of the European Parliament and of the Council; in principle, Regulations of the European Parliament and of the Council are mandatory for all Member States [3]. On 25 and 26 March 2020, four EU countries (Estonia, Greece, Netherlands and Romania) requested an opinion on the CU for remdesivir from the EMA Committee for Medicinal Products for Human Use (CHMP), in accordance with Article 83(3) of Regulation (EC) No 726/2004 [7]. The legal basis for this application refers to: Article 83(3) of Regulation (EC) No 726/2004. The CHMP supports this position and considers that the CU programs should be used for patients who do not participate in a clinical trial.

While the number of critically ill COVID-19 patients in Bulgaria is not comparable with the ones observed in USA, Italy, Spain and France, it is extremely important to ensure the early and expanded access for Bulgarian patients to investigational drugs through CU. Unfortunately, the dearth in the existing national regulation in Bulgaria leads to delayed or difficult access to investigational drugs via CU programs, as well as exclude many patient groups who

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are unable to fulfill the eligibility criteria of clinical trials, and consequently restrict them from early access to promising drugs and hopeful treatments [3]. Remdesivir, also known as GS-5734, has been recognized as a promising antiviral drug, originally developed for the treatment of Ebola virus infection [8]. While it did not prove efficacy in human clinical trials for this disease, it has shown efficacy against RNA viruses (including SARS/MERS-CoV5), Paramyxoviridae (such as Nipahvirus, respiratory syncytial virus, and Hendra virus). Remdesivir is an adenosine analog that incorporates into nascent viral RNA chains and results in pre-mature termination. It appears to have a favorable clinical safety profile, as reported in multiple case reports and randomized trials of Ebola virus disease. It has thus garnered significant attention for its potential use as a treatment option for COVID-19.

Grein, et al. [9] reported data for 53 of 61 patients with COVID-19 who received remdesivir on a CU basis in over 20 hospitals on three continents. Patients received a 10-day course of remdesivir (Gilead Sciences, Inc.), consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation were extubated. A total of 25 patients (47%) were discharged, and 7 of them (13%) died. Mortality among patients receiving invasive ventilation was 18% (6 of 34) and 5% (1 of 19) among those not receiving invasive ventilation. The overall probability of improvement by 18 days was 68% (95% confidence interval 40% to 80%). Thirty two (60%) patients demonstrated at least one adverse event and 12 (23%) patients experienced serious adverse events.

However, the interpretation of the preliminary outcomes of this report is limited due to the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the CU program, the lack of information on eight of the patients initially treated, and finally the lack of a randomized control group.

Unlike to exponential growing requests from clinicians globally for CU, no requests for investigational antiviral drugs (e.g. remdesivir) for COVID-19 were submitted from the Bulgarian clinicians and hospitals. This is because remdesivir is not approved by the FDA, EMA and BDA, and this medication may only be obtained through participation in registered clinical trials or via CU request to the manufacturer (Gilead Sciences, Inc.).

We suggest that COVID-19 pandemic will initiate a dialogue among health policy makers and BDA for the establishment of new health policy and clear national regulation due to higher demand for CU of unauthorized drugs. Both must take further steps for the implementation of a new law regarding CU, considering the benefits and the risks of having an early access to investigational drugs. The regulation update will help the Bulgarian health policy makers and BDA to provide a quick and efficient response to patients’ needs and demand to investigational drugs via CU programs. Finally, the COVID-19 outbreak provides an excellent opportunity to reflect on current needs and gaps in the existing national regulation regarding CU [10]. It is also timely to consider the readiness of the Bulgarian health care system to meet the challenges, new and unexpected threats and risks, both as regards problems and solutions. The update of the existing national regulation regarding CU is vital to ensure effective and sustainable development and delivery of health policy and technology over the COVID-19 pandemic and beyond.

Author Statements

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Competing interests

None declared.

Ethical approval

Not required.

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