

COVID-19 – Therapeutic controversies. The case of ibuprofen

Camil-Eugen VARI, Alexandra GROSAN, George JITCA, Bianca-Eugenia ȐSZ

*Department of Pharmacology and Clinical Pharmacy,
"George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tg. Mures, Romania*

ABSTRACT

Shortly after the declaration of the SARS-CoV-2 infection pandemic by the World Health Organization (WHO), a controversy erupted over the worsening of the disease by NSAIDs, particularly ibuprofen. The premise of this concern was the increase in expression of the ACE2 enzyme in epithelial cells by chronic treatment with ibuprofen; this enzyme is used as a gateway by the virus. Reality and clinical experience have refuted this hypothesis, a fact certified by the regulatory authorities in the field of medicine (EMA – European Medicines Agency, FDA – Food and Drug Administration). Clinical experience suggests exactly the opposite, and the possible protective effect against acute respiratory distress syndrome (ARDS) is currently being investigated in an ongoing clinical study, which is expected to be completed in May 2021.

Keywords: COVID-19, ibuprofen, EMA, FDA, pandemics

INTRODUCTION

The evolution of the pandemic caused by SARS-CoV-2, from the first cases identified at the end of 2019 in Wuhan, China and until today, has found the academic world, researchers and the university elite unprepared. Even at the level of competent or regulatory authorities (WHO, FDA, EMA) the messages were divergent, and their takeover by the media and the marked interest of public opinion made these initial contradictions lead to a decrease in public confidence in the officially provided data and to facilitate the emergence and spread of conspiracy theories. Also, prestigious medical journals, under the pressure of time and to gain

precedence over the competition, have “eased” the conditions of analysis of articles, especially in terms of time allotted and the quality of peer review analysis. As a result, numerous studies have been published, initially in the form of medical hypotheses, which were based on small samples, and then in turn these studies were validated/ invalidated by others. Unlike in normal times, when controversies were maintained in the small circle of researchers, these clinical trials and case reports were heavily publicized, as the press and television “looked at them” and government or regulatory decisions were based on insufficiently verified documentation. In view of these

considerations, we will review the published data on the safety of ibuprofen as a symptomatic medication in the condition caused by COVID-19.

TIMELINE

The mechanism of infection in SARS (severe acute respiratory syndrome, epidemic in 2002) caused by SARS-CoV-1 virus was already known, and it was similar for SARS-CoV-2. These coronaviruses, whose primary host is the bat, infect susceptible human cells via ACE2 (angiotensin-converting enzyme 2); this enzyme is intensely expressed by epithelial cells at the nasal, pulmonary, but also vascular, renal, and intestinal level. ACE2

expression is increased in diabetic patients, in hypertensive ones treated with conversion enzyme inhibitors (ACE inhibitors) or sartans, but also by chronic treatment with thiazolidinediones or NSAIDs (ibuprofen/ ketoprofen) [1,2]. As a result, Fang L. et al., in a correspondence to The Lancet, hypothesize that medication that increases ACE2 expression may be responsible for the more severe course of COVID-19 disease in patients treated in this way [2].

Here is a brief chronology of the facts:

- March 11, 2020 - letter from Fang L. et al. is published online in The Lancet [2];
- March 14, 2020 - French Health Minister Olivier Véran, quoted by Le Monde and later taken over by the world's media, issues a report that does not encourage the use of NSAIDs as a self-medication in treating the symptoms of SARS-CoV-2 infection and supports the use of paracetamol (it is also recommended, on the same occasion, to avoid corticosteroid therapy without strict indication) [3]; on the same day, the German authorities, fighting against information on a fake clinical trial, reiterated that there was no association between the administration of NSAIDs and the worsening of COVID-19 symptoms;
- March 17, 2020 – WHO, through spokesperson Christian Lindmeier, suggests the use of paracetamol as an antipyretic drug and not ibuprofen, although he points out that there are no studies linking ibuprofen to a worsening or more serious course of the COVID-19 infection; the statement was immediately picked up by print and broadcast media around the world, and

ibuprofen was the subject of undeserved public outrage and was not supported by any medical argument; this media phenomenon was known as #ibuprofen (Carius B et al.) [4];

- March 17, 2020 - The “News” section of the British Medical Journal publishes a warning entitled “Ibuprofen Should Not Be Used for Managing Symptoms, Say Doctors and Scientists”; among other opinions, Charlotte Warren-Gash, Associate Professor of Epidemiology at the London School of Hygiene and Tropical Medicine, is quoted as suggesting the use of paracetamol as an antipyretic and a symptomatic medication in pharyngitis [5,6]; the information will be corrected later in the same journal, also in the “News” section under the title “COVID-19: European drugs agency to review safety of ibuprofen”;
- March 18, 2020 - EMA issues a press release; it is specified: *“There is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19. EMA is monitoring the situation closely and will review any new information that becomes available on this issue in the context of the pandemic”*; however, based on the conclusions of EMA’s safety committee (PRAC) - based in turn on the experience of the French Agency’s pharmacovigilance reports on the worsening of chickenpox and bacterial infections treated with NSAIDs – it is recommended: *“When starting treatment for fever or pain in COVID-19, patients and healthcare professionals should consider all available treatment options including paracetamol and NSAIDs. Each medicine has*

its own benefits and risks which are reflected in its product information and which should be considered along with EU national treatment guidelines, most of which recommend paracetamol as a first treatment option for fever or pain. In line with EU national treatment guidelines, patients and healthcare professionals can continue using NSAIDs (like ibuprofen) as per the approved product information. Current advice includes that these medicines are used at the lowest effective dose for the shortest possible period” [6-9];

- Subsequently, all international regulatory authorities with responsibilities in the field of pandemics (WHO) or medicines (EMA, FDA) stressed that there is no link between the more severe evolution of COVID-19 and NSAID treatment; moreover, both paracetamol and NSAIDs are recommended for the treatment of symptoms caused by SARS-CoV-2: fever, myalgia, headache; also patients under chronic NSAID treatment are warned not to discontinue it as the treated condition may worsen. If the patient wants further information (taking into account the intense media exposure of the subject) it is recommended to consult their general practitioner or pharmacist for an informed and relevant opinion in this situation [9-14]. This point of view was also adopted by the Romanian Chamber of Pharmacists.

EXPERT OPINIONS

Since the declaration of the pandemic by the WHO, expert opinions on the use of NSAIDs in SARS-CoV-2 infection have been divided. However, NSAIDs are widely used in the symptomatic

treatment of upper respiratory tract infections such as influenza, the common cold; there are many combinations of NSAIDs (especially ibuprofen) with systemic decongestants (pseudoephedrine, phenylephrine) intended specifically for this purpose (“cold and flu medicines”). Previous pharmacovigilance studies in France have shown that the use of NSAIDs (in chickenpox and certain bacterial infections) can mask the symptoms of the infection (fever, inflammation); as a result, it may delay a correct diagnosis of pneumonia and the adoption of appropriate therapeutic measures. However, discontinuation of chronic NSAID treatments (as well as antiangiotensin medication that increases ACE2 expression such as ACE inhibitors or angiotensin receptor blockers – ARBs) is not indicated, which may worsen the condition of chronic patients [10].

Although COVID-19 disease has many forms of manifestation and nonspecific symptoms (fever, dry cough, rhinorrhea, ageusia, anosmia, diarrhea etc.), severe forms of the disease are manifested by coagulation disorders (which required the routine use of anticoagulants such as fractionated heparins) and severe pneumonia. The most severe forms of lung damage are caused by the cytokine storm, but the role of NSAIDs in this case is unclear, no link can be highlighted [15].

Moreover, severe forms with obvious lung inflammation or consecutive to the cytokine storm benefit from anti-inflammatory therapy, but not from NSAIDs, but from corticotherapy - dexamethasone (Randomized Evaluation of COVID-19 Therapy -RECOVERY- trial of dexamethasone in patients hospitalized with COVID-19) [16] and tocilizumab [17-19].

Tocilizumab is a humanized monoclonal antibody antireceptor interleukin 6, used as an immunosuppressant whose official marketing authorization includes severe rheumatoid arthritis unresponsive to other medicinal products [20].

DATA FROM CLINICAL TRIALS

A retrospective *in silico* study (medical record analysis from 5 Eastern Massachusetts hospitals) on 2,271 patients tested positive for SARS-CoV-2 (707 hospitalized, 213 mechanically ventilated) showed that previous exposure to ibuprofen (along with naproxen, oseltamivir, atenolol) was associated with a lower risk of hospitalization. In addition, even though the statistical power was low, ibuprofen decreased the need for mechanical ventilation (odds ratio 0.47, with a 95% confidence interval 0.14-1.05) [21-22]. In a cohort study conducted in Israel at Shamir Medical Center on 403 COVID-19 positive patients, previously and during treatment with ibuprofen, the main objective was mortality and the need for mechanical ventilation and oxygen therapy (safety study); the administration of paracetamol or ibuprofen for the treatment of fever did not adversely alter the course of the disease or lead to the need for artificial ventilation. In the ibuprofen group mortality was 3.4% compared with 2.8% in the non-ibuprofen group (including patients treated with paracetamol), the difference being statistically insignificant ($p = 0.95$). Final conclusion of the study: no difference was observed between paracetamol or ibuprofen/ or the lack of an antipyretic regarding the mortality rate or the need for ventilation/ oxygen therapy [23].

There is currently an ongoing clinical trial at Guy's & St. Thomas Hospital by King's College of London – acronym LIBERATE – which aims to assess the reduction in the progression of lung damage following the administration of 3 different doses of ibuprofen; an innovative pharmaceutical form is used - Lipid ibuprofen 200 mg.

The study began in May 2020, the first results being expected in September 2020, and the final ones in May 2021. The characteristics of the study are as follows: prospective, randomized, parallel, double-blind study on 230 adult participants, hospitalized, confirmed with COVID-19. The 2 branches of the study (branch 1: no intervention – standard of care vs

branch 2 – standard of care plus ibuprofen lipid) will be compared for disease progression, respectively time to need for mechanical ventilation, over a period of 14 days). The secondary objectives to be evaluated within 28 days are overall survival, reduction in the proportion of patients in need of respiratory care, length of hospitalization (number of days/ number of days in intensive care unit), number of days without the need for mechanical ventilation, patient profile of serum cytokines. The premise of the study is that ibuprofen administered to patients with COVID-19 would decrease the incidence of cases of acute respiratory distress syndrome (ARDS), a severe complication of pneumonia caused by SARS-CoV-2.

CONCLUSIONS

Non-steroidal anti-inflammatory drugs and, in particular, ibuprofen have been unjustifiably suspected of aggravating the disease caused by SARS-CoV-2, as they increase the expression of the enzyme ACE2, which is used as a gateway to the virus. All clinical data refuted this hypothesis, therefore the regulatory authorities (FDA, EMA, WHO) showed that the use of ibuprofen as a symptomatic medication is not associated in any way with the worsening of the evolution of COVID-19. Furthermore, an ongoing clinical trial (LIBERATE) is evaluating the potential of ibuprofen to reduce the risk of acute respiratory distress syndrome in patients infected with SARS-CoV-2.

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