Non-Steroidal Anti-Inflammatory Drugs in the Fight against COVID-19

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In Italy, a flowchart to be used by General Practitioners for the at-home treatment of patients with COVID-19, has been released. It states that early at-home treatment for SARS-CoV-2 infection is possible due to the availability of specific antiviral drugs to be used in at-risk patients, and that non-steroidal anti-inflammatory drugs (NSAIDs) have an important function in combating the virus. Therefore, the use of NSAIDs is not only rational but also effective in cases that cannot be treated using antivirals.

Keywords: COVID-19 treatment ; non-steroidal anti-inflammatory drugs ; indomethacin

1. Introduction

Between 1991 and 1992 the epidemiologists at McMaster University in Hamilton (Ontario, Canada) published a series of studies in which the statute of evidence-based medicine (EBM) was defined for the first time [1]. EBM refers to the application of the best available research to clinical care, which requires the integration of evidence with clinical expertise and patient values [2]. EBM brought about an epochal turning point in the way medicine is practiced. This approach has simplified and made the way medicine is applied more precise and safer.

Unfortunately, however, between the end of 2019 and the beginning of 2020, it can be found ourselves facing a pandemic for the first time in the modern era, determined by a virus (SARS-CoV-2), little-known, which started in China and spread rapidly around the world. This virus immediately showed that it had rapid diffusibility and high lethality, particularly in older subjects and those with comorbidities [3].

At the time, people had no EBM-supported guidelines to help them deal with COVID-19, the disease generated by the SARS-CoV-2 infection. Therefore, it was necessary to return to doctoring like before the advent of EBM and the guidelines, because to obtain indications based on evidence of effectiveness took time, money, and organization. In the meantime, something had to be done; patients could not be left to their own devices without medical support [4]. Despite this, two fronts of doctors were formed who thought in completely opposite ways, namely, that of doctors closely linked to EBM, who claimed, therefore, not to use untested drugs for this disease, and that of doctors, mostly older, who asserted that it was not ethical not deal with the disease at least by using drugs already on the market, which had a rationale based on their known pharmacological mechanisms [5]. That is, drugs that could logically interfere with the multiplication of the virus and counteract the inflammation and thrombosis that is triggered by the infection, in the hope of preventing worsening of the disease, thus reducing hospitalizations and deaths.

A little-known viral disease had to be treated with all the weapons at the disposal. The weapons to combat viral diseases are first and foremost vaccines (provided they are effective and safe) and antiviral drugs, and, in the case of this virus, drugs that could attenuate, if not completely reset, the pathophysiological mechanisms that it uses to determine aggravation of the disease. Unfortunately, however, from the beginning of the pandemic, the governments in most countries almost exclusively espoused the route of vaccines, even boycotting, openly in some countries, the rational use of potentially effective drugs already on the market, albeit with other indications. Yet, it is now well known that mRNA vaccines against SARS-CoV-2 are difficult to develop, particularly due to the rapid variability of this type of virus, which ends up making vaccines partially ineffective, particularly in preventing virus transmission [6]. Among the various drugs already on the market, people had many drugs available, which, based on their mechanisms of action could be efficacious to counteract SARS-CoV-2 infection, preventing it from worsening. Among them, firstly anti-inflammatory non-steroidal drugs.

2. Non-Steroidal Anti-Inflammatory Drugs in the Fight against COVID-19

It would seem obvious, in light of the fact that the virus can, in some cases, aggravate disease-causing uncontrolled inflammation, up to cytokine storm and thrombosis [7][8], to hypothesize the use of anti-inflammatory drugs aimed at reducing the aggressiveness of the disease, as has already been done for some other diseases such as the flu. However, unfortunately, this thesis was espoused by few, also because, at the very beginning of the pandemic, a warning was issued not to use ibuprofen during COVID-19 because this could lead to a worsening of the disease [9]. Furthermore, the first guidelines issued by the Italian Ministry of Health and the Italian Medicines Agency (AIFA), indicated only the use of paracetamol as symptomatic and to carefully observe the progress of the disease in the first 72 h from the onset of symptoms [10].

However, despite ministerial guidelines, some Italian doctors began using non-steroidal anti-inflammatory drugs in the hope of preventing the development of uncontrolled inflammation in the lungs and vessels. Many of these doctors met in groups, to be able to discuss with each other and to try to determine a common line of conduct. Of these, certainly, the largest group was that of Early Home Therapy for COVID-19 (www.terapiadomiciliarecovid19.org (accessed on 19 April 2020)) founded by a Neapolitan lawyer, Erich Grimaldi, to help treat COVID-19 at home in those patients who could not find help from their general practitioners. The results obtained by this and other groups, as later documented by scientific publications, have been very good, showing a significant reduction in both hospitalizations and lethality, particularly when prompt action was taken at the first onset of symptoms, using non-steroidal anti-inflammatory drugs [11][12][13][14][15]. These results were also obtained in older patients and in subjects with numerous risk factors.

One study published in July 2021 by an important Italian group, reported that effective treatment algorithms implemented based on a pharmacological and pathophysiological rationale can greatly reduce hospitalizations of patients with COVID-19 and that this result has important implications both for patients and the health system [11]. In this case, the treatment consisted principally of anti-inflammatory agents, especially relatively selective cyclooxygenase-2 (COX-2) inhibitors, administered early at the very beginning of the onset of symptoms.

One group also published the results of a retrospective observational study of outcomes and hospitalization rates of patients in Italy with a confirmed diagnosis of early COVID-19 [12]. The study was performed on 158 patients divided into two groups. Group 1 of 85 patients was treated as early as possible (<72 h from the onset of symptoms), while group 2 of 73 patients was treated >72 h after the onset of symptoms, because they consulted the doctor late. The NSAID used in this case was indomethacin at a dose of 75 or 100 mg a day, according to weight <70 or >100 kg, integrated with flavonoids, cardioaspirin, and omeprazole. The results of this study showed a significant reduction in symptom duration and hospitalizations in group 1, indicating the efficacy of the drugs used when they were administered promptly at the early onset of symptoms.

These results were also confirmed by a further retrospective multicenter larger study of 966 patients with COVID-19 treated with different non-steroidal anti-inflammatory drugs (NSAIDs) and of a subgroup of 339 older patients with a mean age of 60 years and with multiple risk factors. Prompt intervention with NSAIDs produced better results compared to later intervention [15].

A further publication by Consolaro et al. evaluated the outcomes, by a matched-cohort study, in 108 consecutive patients with mild COVID-19 managed promptly at home, according to the proposed treatment algorithm and in another 108 patients treated with another therapeutic schedule [13]. This study showed a significant reduction in both symptom duration and hospitalizations in the group treated according to the recommended algorithm. Moreover, in this case, NSAIDs with an action relatively selective on COX-2 were preferred. Another recent paper by Cosentino et al. reports the results of an observational retrospective study performed on data provided by volunteer doctors who belong to the IppocrateOrg Association in Italy, on 392 COVID-19 patients [14]. In this case, the treatment, mostly with early NSAID application, produced a great reduction in hospitalizations with a very low number of deaths.

The results of a randomized double-blind placebo-controlled trial were reported recently, showing that mefenamic acid, a non-steroidal anti-inflammatory drug, markedly reduced the extent of symptoms and the time to reach an acceptable health status of the patients [16].

An attractive opinion article clearly asserted that the early administration of NSAIDs, among others, ibuprofen, in COVID-19 patients is not only safe but may also prevent the occurrence of complications that could worsen the course of the disease, and explained some of the suggested protective mechanisms of NSAIDs [17]. Recently, another important review article on early at-home treatment using NSAIDs in patients with mild-to-moderate SARS-CoV-2 infection was published, reporting that early disease symptoms variably reflect an underlying inflammatory response to the viral infection, and that,

for this reason, the use of NSAIDs in the initial stage of the disease could be a valid therapeutic strategy [18]. In this publication, the authors recognize the validity of the approach pioneered by one group, which includes the use of indomethacin [11].

Most of these studies, although observational and retrospective, demonstrate that the early treatment at home with a NSAID improves the outcomes of the disease reducing the duration of symptoms and the number of patients evolving towards interstitial pneumonia, and both the number of hospitalizations and deaths [11][12][13][14][15]. In addition, one of the studies also reported that in the group of patients for whom the therapy was started within 72 h from the beginning of disease symptoms, a significantly lower number of patients had increased D-dimer levels, as compared with the number of patients for whom the treatment had been started later [12].

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