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LETTER TO THE EDITOR **Open Access**

Official Statement of the section of Clinical Pharmacology of Italian Society of Pharmacology on Non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of complications during infections

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On March 16th, 2020, the French Minister of Health has recommended the use of paracetamol for the treatment of fever in patients with suspected of Coronavirus Disease 2019 (COVID-19) instead of ibuprofen or oral cortisone (1).

In this circumstance, the French Authorities have announced that NSAIDs may worsen the clinical condition of patients with COVID-19 based on the evaluation of 4 young patients affected by a severe and sustained COVID-19, with no comorbidity, and with the NSAID treatment identified as the only risk factor. Immediate was the reply from the Spanish Agency of Medicines and Medical Devices (AEMPS), which underlined that there are no scientific data to support a worsening of the infection with ibuprofen or other NSAIDs. They also announced that the relationship between the infection exacerbation and the use of ibuprofen or ketoprofen is currently evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) (2), and it will be available the next May.

In the literature, conflicting results are available on the association between NSAIDs and infections. Some observational studies showed an increased risk of complications in pediatric patients with flu or infections who take NSAIDs (3,4).

A case series, published on BMJ in 2015, described two cases of H1N1 flu and history of NSAIDs abuse that developed type 1 respiratory failure, which required access to the intensive care (5).

Another study, published on BMJ in 2009, showed that the use of NSAIDs could worsen symptoms of H1N1 infection and predispose to the development of multi-organ failure (6). The main explanation to this result is that the NSAIDs administration, through the alleviation of inflammatory symptoms (fever and pain), could impede the prompt recognition of pneumonia, delaying its diagnosis and treatment (7). The infective inflammatory process starts with the activation of polymorphonuclear neutrophils, recruited at the site of infection, which release reactive oxygen species (ROS), proteolytic enzymes, and antimicrobial peptides. This response also involves the cyclooxygenase type 2 (COX) (8-11). Many studies have instead demonstrated that COX could have a protective role during infections. Specifically, Chen and colleagues showed that non-selective NSAIDs (aspirin and indomethacin) and the selective NSAID (celecoxib) inhibit the virus replication through an increase of nitric oxide levels in a model of vesicular stomatitis (12).

Other studies have demonstrated that COX-2 levels are increased in patients with an active viral infection (13-15), suggesting a possible role for COX-2 inhibitors in the control of viral infection (16, 17). Finally, Amici and colleagues have conducted a preclinical study to evaluate the effect of indomethacin on the replication of Severe acute respiratory syndrome-coronavirus (SARS-CoV).

This study showed an important anti-viral activity of indomethacin that is independent from the COX inhibition (18). In conclusion, today, there is no clear evidence that supports the worsening of clinical conditions in patients with COVID-19 and treated with NSAIDs. No Regulatory Authority, apart from the French one, has contraindicated the use of ibuprofen or other NSAIDs for the treatment of flu symptoms. These drugs must be used according to their approved information and at the lower dose that allows a symptom reduction. Therefore, patients in chronic treatment with ibuprofen or other NSAIDs must continue their treatment as long as the PRAC does not conclude the referral on this potential association (19).

The EMA has recently published some information on the use of NSAIDs in patients affected by COVID-19 underlining the necessity of epidemiological studies to provide evidence to confute/confirm the hypothesis on the protective/damaging role of NSAIDs in patients with COVID-19 (19).

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COMMENTARY Open Access

Commentary on "The Official Statement of the section of Clinical Pharmacology of Italian Society of Pharmacology on Non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of complications during infection"

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The world of to placate the discussion on the use of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with coronavirus disease 2019 (COVID-19), we have to dissect the issue in three different questions:

(**i**) can NSAIDs like ibuprofen or cortisone aggravate the COVID-19 infection?
(**ii**) Is paracetamol (acetaminophen) safer than other NSAIDs to treat the symptoms of the infection, such as the fever?
(**iii**) Can NSAIDs be administered for the treatment of patients with clinically complicated SARS-CoV-2 (also referred to as HCoV-19) infections?

As clearly reported in the letter to the Editor by Capuano et al., (1) the answer to the first question is no because of very few clinical cases not supported by plausible biological mechanisms (2). For the second question, the answer is that paracetamol is not safer than NSAIDs like ibuprofen because they act with a similar mechanism of action, i.e., they inhibit the cyclooxygenase-dependent biosynthesis of prostanoids (3). Thus, considering the available evidence, patients with chronic pain, due to arthritis or a related disease, should continue to be treated with their NSAIDs. However, experts suggest that in general, fever is beneficial in fighting infections (4), thus, people infected with a virus or other

microorganisms should avoid reducing fever for extended periods (except in children, pregnant women, or cardiovascular disease patients) using paracetamol or other NSAIDs. Finally, it is recommended that in patients with clinically complicated SARS-CoV-2 infections characterized by (**i**) kidney function deficiency, where vasodilator prostaglandins contribute to maintaining renal blood flow (5) or (**ii**) with gastrointestinal risk factors, NSAIDs should be avoided because their use might predispose to the side-effects of NSAIDs (6) and there is no evidence of a beneficial effect.

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