Management of Osteoarthritis During the COVID-19 Pandemic

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The pandemic spread of the new coronavirus disease 2019 (COVID-19) infection in China first, and all over the world at present, has become a global health emergency due to the rapidly increasing number of affected patients. Currently, a clear relationship between COVID-19 infection incidence and/or complications due to chronic or occasional treatments for other pathologies is still not clear, albeit the COVID-19 pandemic may condition the treatment strategy of complex disorders, such as osteoarthritis (OA). Importantly, OA is the most common age-related joint disease, affecting more than 80% of people older than the age of 55, an age burden also shared with the highest severity in COVID-19 patients. OA patients often show a large array of concomitant pathologies, such as diabetes, inflammation, and cardiovascular diseases that are again shared with COVID-19 patients and may therefore increase complications. Moreover, different OA treatments, such as NSAIDs, paracetamol, corticosteroids, opioids, or other molecules have a wide array of iatrogenic effects, potentially increasing COVID-19 secondary infection incidence or complications. In this review we critically analyze the evidence on either negative or positive effects of drugs commonly used to manage OA in this particular scenario. This would provide orthopedic surgeons in particular, and physicians, pharmacologists, and clinicians in general, a comprehensive description about the safety of the current pharmacological approaches and a decision-making tool to treat their OA patients as the coronavirus pandemic continues.

Aim of the review

Due to the expected residency of the coronavirus disease 2019 (COVID-19) pandemic in the next months or years, the conservative therapeutic approach for the treatment of patients affected by osteoarthritis (OA) would need an adjustment so as not to expose patients to additional risks. The purpose of this review is, beyond presenting an overview of the most-prescribed molecules in everyday practice and those envisioned as future therapeutic options, to provide orthopedists with some guidelines on the management of osteoarthritic patients during this COVID-19 era. In particular, the susceptibility to COVID-19 life-threatening complications and the potential increment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) morbidity/mortality incidence will be discussed to provide a roadmap to orthopedic surgeons about the safety of treatments as well as the possible need for their discontinuation. This is especially important since many patients will need to receive multiple drugs over the course of their disease, and more in general, as the coronavirus pandemic continues. Also, since the discussed OA comorbidities and therapeutic options are also faced by the general population with OA-unrelated inflammatory and/or age-related pathologies, the proposed indications will be a useful outline for general practitioners and specialized clinicians of other branches of medicine in the era of the COVID-19 pandemic.

Osteoarthritis pathophysiology: The role of inflammation

OA is the most common degenerative disease of the joint that impairs quality of life and leads to important disability.[1] Although the disease pathophysiology is still poorly understood and under investigation, it is accepted that the origin of OA is multifactorial. Inflammation, biomechanical alterations, and the immune response play an important role.[2] Indeed, risk factors are sex, obesity, genetic factors, and mechanical factors.[3]

In the development of OA, the whole joint undergoes a complex remodeling, which in turn ends in degeneration. Common histopathological findings in OA are articular cartilage damage, subchondral bone sclerosis and osteophyte formation, joint capsule hypertrophy, and periarticular muscle dysfunction,[4] as well as inflammation of the synovium. Synovitis is in fact a hallmark of OA, characterized by increased vascularization, infiltration of macrophages and lymphocytes, and villous hyperplasia.[4] The inflamed synovium secretes several cytokines and chemokines, which sustain inflammation and contribute to cartilage degeneration and subchondral bone changes. Among cytokines, the most studied are interleukin 1 β (IL-1β) and tumor necrosis factor α (TNF-α),

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which can activate cartilage matrix degeneration by activation of toll-like receptors (TLRs).[5] Moreover, IL-15 and IL-17 are also secreted by the synovium lymphocytes and are associated with OA progression by inducing chemokine production by synovium fibroblast and chondrocytes.[5]

In articular cartilage, the degenerative process is initiated by biomechanical stress and inflammation.[6] Both these stimuli activate the canonical nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), stress-induced and mitogen-activated protein kinase (MAPK) pathways, which trigger the inflammatory cascade and matrix degradation via matrix metallopeptidases (MMPs) (especially MMP-13), nitric oxide synthase 2 (NOS 2), cyclooxygenase 2 (COX-2), hypoxia inducible factor 2α (HIF-2α), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4,5.[4] In addition, chondrocytes undergo hypertrophy through the activation of the canonical Wnt signaling pathway and the consequent upregulation of β-catenin.[7] Lastly, OA is also associated to an increased chondrocyte apoptosis: Cell death may be caused by an HMGB-1-mediated mitochondrial dysfunction, which leads to secretion of reactive oxygen species, prostaglandins, and nitric oxide, and, ultimately, to oxidative stress. The products of this catabolic process (i.e., small pieces of collagen, fibronectin, and proteoglycan) amplify the inflammatory response in cartilage and synovium by inducing innate immune responses through the complement pathway modulation.[8]

Eventually, subchondral bone is also subjected to profound changes in OA that essentially lead to sclerosis, microfractures, and osteophyte formation. The excessive and repetitive mechanical stress causes some initial microfractures, which trigger bone remodeling through the OPG/RANK/RANKL (osteoprotegerin/receptor activator of nuclear factor κB/RANK-ligand) triad, MMPs, IL-6, and IL-8.[4] At the same time, vascular endothelial growth factor (VEGF) expressed by hypertrophic chondrocytes maintains bone remodeling by recapitulating endochondral bone formation. Moreover, recent data show that sclerostin, a Wnt pathway inhibitor, is downregulated in some subchondral areas, causing local bone sclerosis.[9] Finally, osteophyte formation represents an attempt to restore the normal mechanical loading through endochondral bone formation, and it is triggered by transforming growth factor β (TGF-β) and bone morphogenetic protein 2 (BMP-2), which are released by synoviocytes and chondrocytes.[10]

Hence, in the osteoarthritic joint the cross talk between these three main tissues causes a vicious cycle that progressively sustains and amplifies the inflammatory and degenerative processes.

COVID-19 infection pathophysiology

The COVID-19 pandemic represents an unprecedented and largely unanticipated challenge for healthcare systems and professionals worldwide. It is caused by SARS-CoV-2 infection, a novel coronavirus of zoonotic origin, and symptoms include fever, dyspnea, fatigue, dry cough, olfactory and gustatory dysfunction, lymphopenia, and, in the most severe cases, interstitial pneumonia with alveolar damage.[11] According to the John Hopkins Coronavirus Research Center, 2.3 million people has been infected since the beginning of the SARS-CoV-2 outbreak, with more than 155,000 confirmed deaths as of April 20, 2020.[12] Nevertheless, some estimations outnumber the confirmed cases by orders of magnitude, with the possible prevalence of infection up to 10% of the population in some countries,[13] and it is highly likely that a wide portion of individuals suffering from other common conditions, such as osteoarthritis, may have been infected by SARS-CoV-2. In particular, OA is more frequent in the elder population, a category that is at high risk of infection, given the more frequent need for health care and hospitalization, as well as more subjected to severe or fatal outcomes following SARS-CoV-2 infection.[14]

The molecular mechanisms of SARS-CoV-2 infection have been partially elucidated by recent reports that identified the angiotensin-converting enzyme 2 (ACE2) as the host cell surface receptor allowing for the viral infection.[15] This protein is expressed in a number of tissues, including alveolar epithelial cells, vascular endothelium, and oral mucosa, and it is responsible for the cleavage of angiotensin I and angiotensin II,[16] playing a regulatory function in the heart[17] and possibly a protective role in lung diseases.[18] COVID-19, similarly to other viral infections, such as SARS-CoV in general and H5N1 in particular, causes a decrease of ACE2 expression, partially explaining the severity of the lung damage in the pathology.[19,20] Then, the treatment of pathologies such as hypertension, requiring ACE inhibitor administration, may accelerate the progression of the pathology, even if the evidence is still insufficient to balance the cost/benefit equilibrium towards the suspension of these therapies in all patients undergoing this treatment.[21] In this frame of cost/benefit balance, ACE inhibitors also lead to upregulation of *ACE2* expression,[22] eventually dealing with a double-edged sword by increasing protection for lung tissue function at the cost of potentially increased infectivity. Besides the initial phase of SARS-CoV-2 infection, COVID-19 pathology may exhibit three grades of increasing severity, from early infection to pulmonary involvement and eventual systemic hyperinflammation.[23] Usually the grades are associated with the upregulation of proinflammatory cytokines, such as IL-1β and IL-6, IL-2, IL-8, and TNF-α, or chemokines, that are significantly elevated in those patients with a more severe disease.[23] The high levels of these cytokines have been also reported to be inversely related to the absolute lymphocyte count.[24] Since an effective immune response against viral infections depends on cytotoxic T-cell activation,[25] experimental evidence supports the observation that overexpression of inflammatory cytokines like IL-6 during the viral immune response might be associated with a decreased viral clearance by impairing the polarization and functionality of type 1 helper T cells and CD8 cells,[26] contributing to the worsening of the COVID-19 symptoms, and their management may appear an intriguing therapeutic approach. Overall, the administration of drugs for the control of inflammation, inhibiting the response of the immune system, may be detrimental in the initial phases of the viral infection, reducing the ability of the body to react to the presence of SARS-CoV-2, as observed in patients chronically treated for rheumatoid arthritis.[27] On the other hand, this action may be beneficial in the reduction of the cytokine and chemokine excess, responsible for the worsening of the clinical picture. Indeed, drugs managing cytokines which are known to

increase during the COVID-19 infection, as IL-6 and TNF-α, were postulated as possible effective treatments to counteract the immunopathological manifestations of the COVID-19 infection based either on *in vitro* and *in vivo* data, as metronidazole (reducing several inflammatory cytokines like IL-6 and TNF-α),[28] or on preliminary good response, to be evaluated with caution and confirmed, in the treatment of a small cohort of COVID-19 patients, as tocilizumab (a monoclonal antibody against IL-6) that was used in combination with methylprednisolone.[29] Therefore, in the context of COVID-19 patients, the governance of the cytokine crossroad and inflammation is one of the major unmet needs, together with the adjunctive chronic or acute comorbidities and the effects of drugs administered for their management.

OA AND COVID-19

Predisposing comorbidities in OA patients

At the moment, no studies have investigated a potential relationship between respiratory viral infections and the development of OA, as described for parainfluenza and coronavirus and the incidence of rheumatoid arthritis.[30] Similarly, looking the other way round, there is no documented increased risk of respiratory infections for OA patients compared with the general population.

Comorbidities are another factor tipping the balance towards an increase of morbidity and mortality during infections. In OA patients, several concomitant disorders, such as obesity, low muscle mass, hyperuricemia in women, diabetes, hypertension, and cardiovascular diseases (CVDs) are present at a higher ratio than in the general population.[31] A recent meta-analysis showed that the most prevalent COVID-19 comorbidities were hypertension, cardiovascular diseases, and diabetes mellitus,[21,32] and their presence increased life-threatening complications. In this frame, it was recently reported that obesity may be a trigger to COVID-19 morbidity and mortality.[33] Similar outcomes are expected also for diabetes patients,[34] following what was stated for the two earlier CoV infections, SARS in 2002[35] and the Middle East respiratory syndrome (MERS) in 2012.[36] Consistently, a recent report indicated diabetes as a risk factor significantly associated with unfavorable COVID-19 clinical outcomes.[37] Also, arterial hypertension may be associated with increased risk of mortality in hospitalized COVID-19–infected subjects.[38] Regarding CVD, preexisting cardiovascular pathologies increase the morbidity and mortality of COVID-19, and COVID-19 itself causes serious cardiac sequelae.[39] As a consequence, although a direct relationship between COVID-19 mortality and morbidity in OA patients has not been reported yet, the presence of OA-related concomitant disorders might trigger the life-threatening risks for OA patients in case of SARS-CoV-2 infection. This shall prompt orthopedists and clinicians in general to evaluate with extreme care the clinical conditions of OA patients not only from the perspective of OA symptom management but also for undercurrent comorbidities, naturally occurring or OA-treatment-related, that, in the era of COVID-19 pandemic, may strongly affect patient outcomes more than the net combination of SARS-CoV-2 infection and OA. This paradigm is valid also for other pathologies characterized by comorbidities similar to those herein discussed or other conditions reported to affect COVID-19 trajectory.

OA drugs and viral infections: What do we know?

Nonsteroidal antiinflammatory drugs (NSAIDs). International and national guidelines recommend NSAIDs for the treatment of severe pain and musculoskeletal pain in OA patients.[40] NSAIDs are the most commonly prescribed drugs, used by 60% of OA patients taking medication in Europe[41] and more than 50% across the United States.[42] NSAIDs may be divided into nonselective (nsNSAIDs), targeting both cyclooxygenase (COX)-1 and COX-2, and COX-2 selective (sNSAIDs). COX-pathway inhibition leads to decreased production of prostanoids and decreased recruitment of polymorphonuclear neutrophils to the inflammatory site.[43] In general, NSAIDs have been associated with higher frequencies of gastrointestinal, renal, and CVD negative outcomes, with the degree of COX-1 and COX-2 inhibition, and not COX-2 selectivity, being responsible for the increased risk.[44] As previously mentioned, CVD and COVID-19 are directly linked, and the development of kidney failure during hospitalization in patients with COVID-19 is frequent and associated with mortality.[45]

Regarding a major COVID-19 outcome like respiratory tract infections, including complicated pneumonia, pleural effusions, and peritonsillar abscess, NSAID use mainly resulted in an increase of complications. A recent review associated prehospital NSAID exposure with higher risks of a protracted and complicated course of pneumonia, including those in intensive care units.[46] Another population-based study in northern Denmark evaluated NSAID use as a prognostic factor for clinical outcomes in hospitalized patients with pneumonia.[47] All current users, including long-term users, showed an increase in the adjusted rate ratios (aRRs) of pleuropulmonary complications (1.81 (95% confidence interval (CI), 1.60–2.05)). Further, in a trial studying almost 900 patients with respiratory tract infections, 20% of them advised to take ibuprofen were documented to have reconsultations concerning new/unresolved symptoms or complications (aRR of 1.67 (1.12–2.38)).[48] Eventually, in children with upper and lower tract viral infections of diverse etiology, ibuprofen exposure resulted in an increased risk of empyema (aRR of 2.79 (1.4–5.58), $P = 0.004$) caused by *Streptococcus pneumoniae* of different serotypes.[49]

Finally, regarding the role of NSAIDs in viral infections, there is not a clear indication due to lack of clinical evidence. In rats, ibuprofen induced the overexpression of ACE2,[50] and this effect might theoretically worsen the COVID-19 infection.[21] Nevertheless, to date, no conclusive evidence in favor or against the use of NSAIDs during the treatment of COVID-19 patients is available.[51,52] Therefore, a pragmatic and cautionary approach would suggest that clinicians carefully consider NSAID use as the first-line option for managing symptoms, if not absolutely necessary, due to both respiratory and cardiovascular complications in several settings. Regarding pain patients, as OA patients, who are not SARS-CoV-2 infected, they may be reassured by their physicians on the safety of NSAID continuation, because there is nothing conclusive to show the potential for an increased incidence of viral infection, and especially of COVID-19.[53] Conversely, chronic

prehospital NSAID exposure might increase complications like in all other patients, and OA patients with SARS-CoV-2 infection under NSAID treatment should be monitored with additional care and NSAID use considered only when strictly necessary (**Table 1** and **Figure 1**).

Paracetamol. The 2011 National Health and Wellness Survey showed that in 3,750 patients from five European Union countries with self-reported peripheral joint OA, 47% of patients reported prescription medication, with paracetamol ranging from 0% in Germany up to 6% in Spain.[41] Similarly, in the United States, paracetamol was taken by approximately 10% of patients participating in the Osteoarthritis Initiative.[54] The relevance of paracetamol is its use for the longest duration (mean 84 months) and usually for more than 20 days per month,[41] due to its safety at correct dose. Its exact mechanism of action remains to be determined, although its effect on the prostaglandin production also at the level of central nervous system has often been hypothesized. Paracetamol has similar effects to those of the selective COX-2 inhibitors, but without any antiinflammatory capacity.[55] It is generally considered to be safer than NSAIDs, albeit recently increased risk of adverse outcomes with frequent paracetamol dosing was published, including mortality, CVD, and renal adverse events.[56] Moreover, acute liver injury resulting in relevant liver function abnormalities (bilirubin ≥ 3 mg/dL, alanine aminotransferase (ALT) > 5× the upper limit of normal (ULN), alkaline phosphatase > 2× ULN) is not uncommon with therapeutic doses of paracetamol in patients without other possible causes of liver injury,[57] as well as a general alteration of liver functionality (ALT > 3× ULN) even in healthy subjects without acute liver injury symptoms or laboratory evidence of hepatic failure.[58] Also, the development of liver diseases during hospitalization in patients with COVID-19 is high and associated with mortality.[59] Therefore, how underlying liver conditions may influence the onset of hepatic complications in patients with COVID-19 and their association with the use of drugs need to be meticulously evaluated.

Regarding respiratory tract infections, a paucity of data is reported and is related to paracetamol effect on disease complications rather than incidence. In the previously mentioned trial for ibuprofen,[48] paracetamol showed a better performance, with only 12% of patients documented to have reconsultations concerning new/unresolved symptoms or complications (aRR of 1, control group). Moreover, in the Northern Denmark population study to evaluate antiinflammatory/analgesics use as a prognostic factor for clinical outcomes in patients hospitalized with pneumonia, differently than for NSAIDs, an association with pleuropulmonary complications in users of paracetamol was not observed (aRR of 0.97 (0.86–1.09)).[47] Overall, paracetamol might be a better option in case of pneumonia due to NSAIDs' detrimental consequence

Table 1 Potential role of OA drugs in COVID-19 pandemic and major related events

Molecule	Main iatrogenic effects	Respiratory tract infections	Interaction with coronavirus	Indication for OA patients
NSAIDs	Gastrointestinal, renal, and CVD[44]	Increased complications, bronchoconstriction[46-48]	Increase of ACE2 in rats.[50] No conclusive evidence for COVID-19[51]	No evidence for discontinuation – Balance cost/benefit for patients with weak symptoms
Paracetamol	CVD, liver, and kidney at high doses[56,57]	No reported risks[47] – Reduced morbidity in mice with Influenza A[61]	No evidence	No evidence for discontinuation
Corticosteroids	Diabetes and hyperglycemia, CVD, and immunosuppression for systemic use[67]	Controversial effects. Both reduced[70] and increased complications and mortality with pneumonia were reported[75]	Controversial effects. Delayed virus clearance for SARS[74] and MERS[73] but reduced mortality with SARS.[77] No association with virus clearance and duration of symptoms in COVID-19[80]	No evidence for discontinuation for systemic treatment – Balance cost/benefit for patients with weak symptoms
Opioids	Abuse and misuse,[93] constipation, nausea/vomiting,[94] respiratory depression.[85] Increased risk for general AEs in OA patients.[91]	Depends on immunosuppressive (IS) and/or weak/strong activities. Absence of IS and/or weak activities are related with reduced pneumonia incidence[86,89,90]	Strong and/or IS opioids could potentially be more susceptible to COVID-19 complications like pneumonia, but no direct evidence is reported	No evidence for discontinuation – When needed, weak opioids with no IS activity should be preferred
mAbs	Generally safe. CVD and infections in general[114]	Increased influenza-like illness[115]	Anti–TNF-α mAb may reduce ACE2 expression.[122] Anti–IL-1β may be beneficial for coronavirus-related complications[126]	No evidence for experimental use of mAbs in OA and COVID-19 patients except compassionate use

ACE2, angiotensin-converting enzyme 2; AEs, adverse events; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; IL, interleukin; MERS, Middle East respiratory syndrome; mAbs, monoclonal antibodies; NSAIDs, nonsteroidal antiiflammatory drugs; OA, osteoarthritis; SARS, severe acute respiratory syndrome; TNF, tumor necrosis factor.

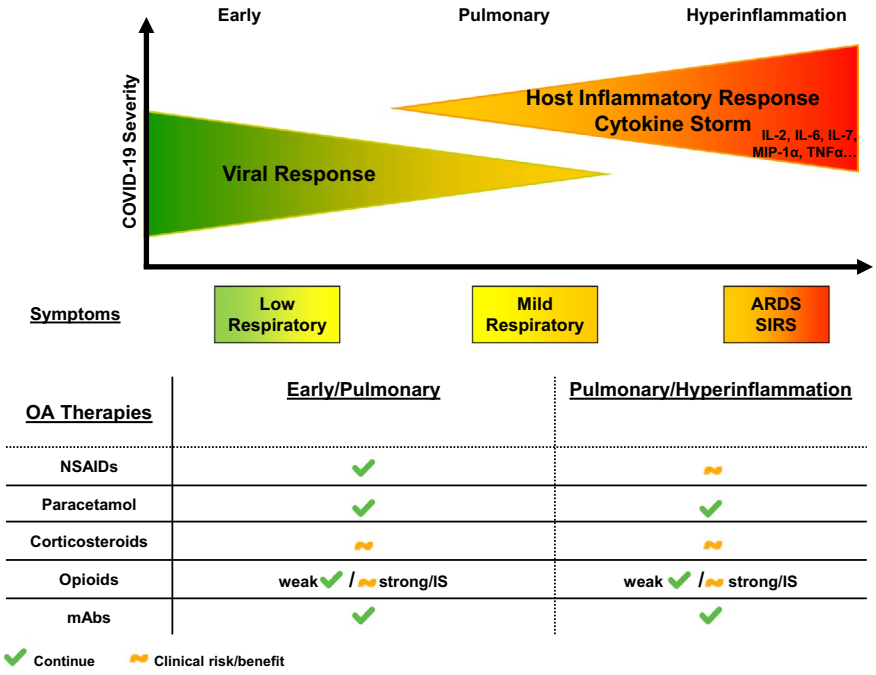

Figure 1 Classification of COVID-19 disease states and overlay with OA-associated treatments. The figure shows the escalating phases of disease progression with COVID-19, with associated symptoms and the relevance of OA treatments with their possible continuation, discontinuation, or cost/benefit depending on available literature data. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; IL, interleukin; IS, immunosuppressive; mAbs, monoclonal antibodies; MIP, macrophage inflammatory protein; NSAIDs, nonsteroidal antiiflammatory drugs; OA, osteoarthritis; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor. [Colour figure can be viewed at wileyonlinelibrary.com]

of delaying antibiotic therapy and bronchoconstriction, possibly leading to NSAID-exacerbated respiratory disease phenotype that, when diagnosed, results in NSAIDs discontinuation.[60]

For respiratory tract viral infections, in a mouse study it was reported that paracetamol reduces the morbidity associated with Influenza A infection by decreasing the infiltration of inflammatory cells into the airway spaces and improving the overall lung function.[61] In a Cochrane Review, paracetamol helped relieve nasal obstruction and rhinorrhea but did not appear to improve sore throat, malaise, sneezing, and cough in people with cold, the most frequent viral infection of the upper respiratory tract.[62]

In conclusion, in the COVID-19 frame, at present there is no evidence in favor or against the use or a higher safety profile of paracetamol vs. NSAIDs during the treatment of patients. Surely, those already taking paracetamol should not discontinue its use, although it should be taken into account that, likewise with NSAIDs and other antipyretic substances, paracetamol does not increase infectious risk ratio but can be responsible for a later presentation of symptoms or an underestimation of the severity of the disease, both leading to a delayed diagnosis, possibly a worse prognosis, and life-threatening complications (**Table 1** and **Figure 1**).

Corticosteroids. Corticosteroids (CSs) are potent multitargeting antiinflammatory drugs.[63] In OA patients, CSs are administered both systemically and, more often, intraarticularly. Among others, prednisone is the most prescribed systemic steroid,[64] and few other molecules have US Food and Drug Administration (FDA) (methylprednisolone, triamcinolone, betamethasone, and dexamethasone) or European Medicines Agency (EMA) (methylprednisolone, triamcinolone) labels for intraarticular injections.[65] CSs have both antiinflammatory and immunosuppressive effects, and their mechanism of action is complex. It includes inhibition of accumulation of inflammatory cells, metalloproteases, and metalloprotease activators, and synthesis and secretion of proinflammatory factors.[66] Long-term systemic (oral or parenteral) use of these agents is associated with adverse events such as diabetes and hyperglycemia, osteoporosis, superinfection, CVD, and immunosuppression.[67] For intraarticular administration, adverse events are less likely, probably due to serum cortisol levels decreasing within hours and recovery to baseline in 1–4 weeks. Nevertheless, intraarticularly administered CS resulted in reduction of inflammatory markers like C-reactive protein and erythrocyte sedimentation rate that can last for months, and in a transient increase in blood glucose levels in diabetic OA patients,[68] despite this treatment often showing short-term benefits. To avoid this pitfall, triamcinolone acetonide extended release, produced using microsphere technology, was recently approved by the FDA, given the significant improvement over placebo and even reduced systemic exposure compared with immediate-release triamcinolone.[69]

In the context of pneumonia, a recent Cochrane Review analyzed 28 studies evaluating systemic CS therapy, given as adjunct to antibiotic treatment, vs. placebo or no corticosteroids for adults and children with community-acquired pneumonia.[70] The combined therapy after infection reduced mortality and morbidity in adults with severe pneumonia, and morbidity, but not mortality, for adults and children with nonsevere pneumonia. Hyperglycemia

was indicated as the main adverse event, as also emerged in another review covering four clinical trials for pneumonia patients.[71]

Regarding respiratory tract viral infections and CS influence on complications and life-threatening events, the situation is more controversial. Corticosteroids were widely used during the outbreaks of 2002 SARS-CoV[72] and 2012 MERS-CoV.[73] For SARS, in a randomized controlled trial to compare the plasma SARS-CoV RNA concentrations in ribavirin-treated patients who received early hydrocortisone therapy (< 7 days of illness) with those who received placebo, the nine patients who received hydrocortisone (mean 4.8 days (95% CI, 4.1–5.5) since fever onset) had greater viremia in weeks 2 and 3.[74] In the MERS study in 309 patients, CS therapy was not significantly associated with 90-day mortality (adjusted odds ratio of 0.75 (0.52–1.07), $P = 0.12$) but was associated with delay in MERS coronavirus RNA clearance from respiratory tract sections (adjusted hazard ratio (aHR) of 0.35 (0.17–0.72), $P = 0.0005$).[73] In a systematic review and meta-analysis covering 6,548 patients with influenza pneumonia, CSs were associated with higher mortality (aRR of 1.75, (1.30–2.36), $P = 0.0002$) and a higher rate of secondary infection (aRR 1.98 (1.04–3.78), $P = 0.04$).[75] Additionally, in 50 patients with respiratory syncytial virus infection, those who received steroids had an impaired antibody response, although no significant differences in viral load peak were reported.[76] Conversely, other studies supported the use of corticosteroids at low-to-moderate dose in patients with SARS infection. In a retrospective study in 401 patients, CSs were shown to contribute to lower overall mortality, lower instant mortality, and shorter hospitalization stay ($P < 0.05$).[77] Also, in a prospective cohort study enrolling 2,141 patients with influenza A(H1N1) pdm09 viral pneumonia, low-to-moderate-dose (25–150 mg/day) CSs were related to reduced 30-day mortality (aHR of 0.64 (0.43–0.96), $P = 0.033$)).[78] Overall, the recent guidelines from the American Thoracic Society and the Infectious Diseases Society of America advise against adjunctive CS treatment of pneumonia or influenza pneumonia except in patients who have other indications for their use.[79]

Eventually, in April 2020 the first report on COVID-19 patients treated with CSs after infection was released.[80] Eleven patients out of 31 received CSs, and no association was indicated between CS treatment and virus clearance time (HR of 1.26 (0.58–2.74)), hospital length of stay (0.77 (0.33–1.78)), or duration of symptoms (0.86 (0.40–1.83)). Therefore, again, no clinical data that exist at the moment suggest that a net benefit or detriment is derived from CSs in COVID-19 patients. Some light for future research and eventual indication of CS use for COVID-19 might be related to their antiinflammatory and immunosuppressive effects, since the most obvious detrimental outcomes on the immune system might be balanced by the reduction of the cytokine storm associated with COVID-19 progression. At present, in absence of clear indications, in the last update of World Health Organization (WHO) guidelines for patients suspected of COVID-19 infection, as for general or influenza pneumonia it is recommended to avoid routine CS use unless it is indicated for another reason.[81] In this scenario, in OA patients already treated systemically with CSs,[82] there is no clear evidence suggesting the need for discontinuation, due to absence of clinical data connecting CS therapy and increased COVID-19 incidence. For intraarticular injections that are usually administered on a cadence basis of few months, semesters or yearly, the presumable interruption in the hospitals' and clinics' non–life-saving treatments during the pandemic should avoid even the smallest and still unreported risk. Again, systemic use, new or continuing preinfection therapy, during COVID-19 infection should be carefully monitored for potential complications and, if possible, reduced to a minimum. (**Table 1** and **Figure 1**).

Opioids. Opioids may be a valuable treatment option for severe OA pain when other analgesics are contraindicated (e.g., allergic patients or GI problems) or insufficient to control pain. Opioids may be divided into weak, such as codeine and tramadol, or strong, among which morphine, fentanyl, and oxycodone and their analogous molecules are the most common.[83] In general, opioids should be administered with care since they may interfere with the innate and acquired immune response,[84] are associated with respiratory depression,[85] and increase the incidence and severity of infections of the airway's tracts, including pneumonia.[86] Moreover, opioid systems impair and modulate immune responses induced by the influenza virus that, on one hand, might be beneficial for controlling viral immunopathogenesis, but, on the other hand, may lead to delayed viral clearance.[87] Aware of these premises, individual molecules differ in their effects.[88] A group of them (i.e., morphine, fentanyl, and remifentanil) was described as immunosuppressive[88] and their use associated to increased pneumonia incidence compared with molecules with no immunosuppressive activity.[86,89] Also, weak opioids were associated with a reduced risk of hospital-treated pneumonia among Alzheimer's disease patients compared with strong opioids (aHR of 1.54 (1.09–2.17) vs. 2.83 (1.89–4.24)).[90] Moreover, regardless of opioid strength or immunosuppressive features, highest risk was observed during the first two months of use (aHR 2.58, (1.87–3.55)), and disappeared after prolonged use (> 180 days) (0.91 (0.62–1.33)), as for OA patients under chronic management.

In the OA frame, a 2014 Cochrane Review, including randomized or quasi-randomized controlled trials that compared oral or transdermal opioids with placebo or no treatment, demonstrated an increased risk of general adverse events in the opioid group (RR 1.49 (1.35–1.63)).[91] Notably, considering the different administration routes, no differences in the overall adverse event profile emerged between transdermal opiates and oral treatments.[92] Nevertheless, the risk for adverse outcomes due to opioid abuse remains, since more than 20% of OA patients receiving prescriptions have a risk factor for misuse,[93] and associated adverse events (constipation, nausea/vomiting).[94] Being aware of the several molecules used in OA management, we will below report available information about two widely prescribed weak opioids, with and without immunosuppressive activity, due to their possible reduced interaction with respiratory tract infections and their preferential use in place of paracetamol or NSAIDs.

Tramadol is a weak analgesic opioid, without immunosuppressive activity,[88] that is recommended to manage pain in OA patients by both the American Academy of Orthopedic Surgeons[95] and American College of Rheumatology guidelines.[96] In the United

States, tramadol prescriptions were 10% in 2009 for OA patients.[97] Unlike NSAIDs, tramadol does not cause bleeding in the stomach and intestines, or kidney problems. A recent Cochrane Review sifting 22 randomized controlled trials, including 3,871 participants randomized to tramadol and 2,625 controls, indicated nausea, dizziness and tiredness as main adverse events (risk ratio of 1.34 (1.24–1.46) compared with placebo).[98] In a cohort study that included 88,902 OA patients, aged 50 years old and older, and treated with tramadol or nsNSAIDs/COX-2 inhibitors, all-cause mortality was higher for tramadol compared with diclofenac (HR of 1.88 (95% CI, 1.51–2.35)), celecoxib (1.70 (1.33–2.17)), and etoricoxib (2.04 (1.37–3.03)).[99] Mortality rates were also higher in the tramadol cohort for (i) infection (nsNSAIDs: 2.35 (1.38–3.98) vs. naproxen; 1.73 (0.97–3.10) vs. diclofenac) and (COX-2 inhibitor: 2.61 (1.27–5.38) vs. celecoxib; 1.64 (0.57–4.73) vs. etoricoxib), and (ii) respiratory diseases (1.22 (0.67–2.24) vs. naproxen; 2.86 ((1.28–6.41) vs. diclofenac) and (2.27 (1.13–4.56) vs. celecoxib; 4.44 (1.30–15.17) vs. etoricoxib). Nevertheless, because of the relatively small number of deaths from each specific cause, often between 1% and 0.1% per cohort, most associations were not statistically significant.

Codeine is a weak analgesic opioid with immunosuppressive activity. In the United States, codeine was among the five most-prescribed opioids to manage OA pain in the 2003–2008 period.[97] In a double-blind randomized placebo controlled trial of controlled codeine release for OA treatment in 103 patients, constipation, somnolence, and dizziness were the most significant side effects.[100] Although being a weak opioid, but consistent with its immunosuppressive activity, chronic codeine use was associated with higher pneumonia incidence compared with non-use (odds ratio of 1.93 (1.22–3.06)).[101] Again, pneumonia risk was closer to null for use begun more than 90 days prior to index date (odds ratio of 1.27 (0.91–1.77)). Eventually, in chronic consumers, no pattern was seen for pneumonia risk in relation to estimated daily dose,[101] although the risk of adverse events due to abuse or misuse, like dependence and/or constipation, remains.

Regarding COVID-19, it is appropriate to postulate that chronic pain patients, as OA patients, on strong (and/or immunosuppressive) opioids could potentially be more susceptible to SARS-CoV-2 infection complications like pneumonia, whereas weak opioids might have reduced side effects and infection susceptibility and be therefore preferable. Nevertheless, at present, there is not a clear indication for or against opioid discontinuation in relation to increased COVID-19 infection incidence, but surveillance in case of strong drugs should be conducted. (**Table 1** and **Figure 1**).

Monoclonal antibodies. Disease-modifying osteoarthritis drugs (DMOADs) are molecules targeting key tissues in the OA pathophysiology process and aiming to prevent structural progression, control inflammation, and relieve pain.[102] Currently, no DMOADs have been licensed for use in the treatment of OA, but several putative DMOADs are in phase II development. In particular, monoclonal antibodies (mAbs) and inhibitors directed against OA-related cytokines, such as tumor necrosis factor α (TNF-α),[103-106] nerve growth factor,[107-109] or interleukin molecules like IL-1α/β,[110-112] are under investigation, due to their regular use as biological disease-modifying antirheumatic drugs (bDMARDs) for the management of rheumatoid arthritis inflammation.[113] In a report comparing safety outcomes of bDMARDs in rheumatoid arthritis in 42 observational studies, a general safety profile of bDMARDs emerged with very sporadic cases of cardiovascular and infection incidence.[114] Moreover, in a study aimed at evaluating the incidence of influenza-like illness in a group of patients suffering from chronic inflammatory rheumatism and treated with bDMARDs, influenza-like illness occurred at a higher rate than the value reported in the general population, although no important complications or hospitalizations have been reported.[115] Similarly, a very low rate or absence of adverse events was observed for tested DMOADs, like TNF-α,[116-118] nerve growth factor,[108,109] and IL-1α/β[111,112,119] inhibitors, suggesting an overall safety profile.

Their use is therefore envisioned as a cutting-edge approach with lower risks, readily available as soon as efficacy data will be available. Further, and increasing the interest in the field, recent studies indicated a possible link between these treatments and the positive management of COVID-19 infection. For TNF-α inhibitors, TNF-α production has been associated with TNF-α–converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, crucial for the penetration of the virus into the cell.[120] As a consequence, TNF-α inhibitors might interfere with SARS-CoV infection incidence and the consequent organ damage,[121] via TNF-α inhibition and down-regulation of ACE2 expression and shedding, as recently showed in the gut.[122] For these reasons, a clinical study for the efficacy and safety of adalimumab injection in the treatment of patients with severe novel COVID-19 pneumonia is ongoing in China (ChiCTR2000030089). Moreover, a potential role for IL-1β inhibitors or blockers could be envisioned from data showing an activation of the NLRP3 inflammasome by SARS-CoV,[123] with SARS-CoV–infected patients having elevated serum levels of IL-1β.[23] Similarly to other SARS-CoV pathogens, SARS-CoV-2 also triggers inflammasome activation, especially within lymphoid cells, and patients have increased serum IL-1β.[124] Consistently, a Chinese study demonstrated that inhibition of proinflammatory cytokines such as IL-1β might be a beneficial strategy for the treatment of SARS infections.[125] Further, a phase III randomized controlled trial of IL-1β blockade in sepsis showed significant survival benefit in patients with hyperinflammation.[126] Nevertheless, at present, there is no evidence for IL-1β blockers in the treatment of COVID-19 patients. The literature, however, did suggest a potential role for the reduction of proinflammatory markers, such as IL-1β, which are elevated as part of the immune response and may have a role in the severe lung damage associated with human coronaviruses. Under the same paradigm, IL-6 proinflammatory cytokine is under investigation as a target for COVID-19 therapy, particularly in patients developing acute respiratory distress syndrome with severe hyperinflammatory response characterized by high increases of plasma IL-6 and C-reactive protein levels. In very preliminary results of a recent report, IL-6 blocker tocilizumab appeared to be an effective treatment option in COVID-19 patients, although used in combination with glucocorticoids.[29] In conclusion, in the COVID-19 patients with concomitant OA, for which

traditional treatments still have a wider and documented consistency and safety, more data about mAbs efficacy/safety and the completion of DMOADs phase II studies will lay the foundation for the use of these cutting-edge and possibly safer therapeutics as first-line option in the near future, when the pandemic is expected to remain a threat. (**Table 1** and **Figure 1**).

CONCLUSIONS

The data reported in this review partially identify the effects of commonly used drugs on both infection incidence of COVID-19–related pathologies and disease complications (**Table 1** and **Figure 1**). The specific role of antiinflammatory drugs, taken for a long time at high dosage to control OA symptoms, in reducing the immune response but at the same time containing the cytokine storm characterizing the severe COVID-19 disease, is certainly interesting. However, evidence is not clearly defined. Cutting-edge approaches, such as mAbs, probably have lower side effects and more specificity to reduce proinflammatory markers, thus preventing or reducing the most severe outcomes of disease. The introduction of some mAbs in compassionate use for COVID-19 patients showed encouraging results, which can indicate the real consistency with this previously mentioned hypothesis, but, again, this still needs to be studied and confirmed by large epidemiological studies. In this view, we underline the crucial role of the orthopedic registries as an effective collection of evidence in this prominent field.

To face the pandemic at present times, on a daily basis clinicians decide the first-line pharmacological therapy, whether or not to discontinue an existing therapy, and the efficacious alternative when the previous approach fails. Both patients' characteristics (comorbidities) and previous treatments' iatrogenic effects are essential to drive these decisions and reflect perceived differences in safety across drugs for incidence and complications. The currently available data indicate that OA therapies are safe, and there is not any clear indication to avoid prescription or suggest discontinuation of existing pharmacological therapies due to Covid-19 infection incidence or complications. Nevertheless, we are convinced that particular attention should be used for OA patients, especially if hospitalized. In our opinion, specialists and clinicians should carefully consider each single patient profile and balance the cost/benefit ratio of current or new therapies (**Table 1** and **Figure 1**). Often, antiinflammatory and antipain drugs are prescribed for weak-to-moderate symptoms caused by everyday life movements that are largely reduced, if not absent, during home isolation or hospitalization. Therefore, drugs reported to have the strongest supposed influence on secondary infections or complications should be prescribed only when benefits outweigh the potential harm. In this frame, another crucial and still largely underestimated factor for the choice of the most appropriate therapy and its continuation/discontinuation is the stage of the COVID-19 infection (**Figure 1**). In absence of symptoms or in the early/middle stage, especially in younger patients with absence of relevant comorbidities, continuation of OA therapies is strongly recommended since approximately 80% of affected individuals will end in this stage without complications leading to hospitalization/intensive care. In the mild/late phase of infection, characterized by a state of high levels of inflammation leading to further clinical deterioration and potential involvement of extrapulmonary sites, the cost/benefit ratio of OA therapies has to be evaluated with care, especially for CSs or strong/immunosuppressive opioids. In general, with a few exceptions that deserve cost/benefit considerations, OA patients should be reassured to continue their treatment even during the COVID-19 outbreak. This would prevent disease flares that can contribute to increased patient burden, disability, poor quality of life, and healthcare use. At the same time, all physicians are encouraged to keep up to date on new evidence that will emerge from the future epidemiological studies and that may modify the existing knowledge.

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CONFLICT OF INTEREST

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