Corticosteroids
in the therapy of adult patients with COVID-19

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In view of the evolution of knowledge about COVID-19 and the outcome of the recent review carried out by the EMA, pursuant to Article 5(3) of Regulation EC 726/2004, it is considered essential to provide clinical experts with useful information in order to guide prescriptions and to define, for every medicine used, a risk-benefit estimation in individual patients.

Classification Corticosteroids are synthetic medicinal products that mimic the action of natural hormones; they have anti-inflammatory properties and regulate the activity of metabolism and immune system. They are widely used in current clinical practice, for example in case of chronic inflammation, allergic reactions and autoimmune diseases. Their role in the treatment of serious infections of bacterial or viral origin has always been controversial in literature.	
Why are corticosteroids considered useful for the treatment of COVID19?	***Rationale*** Because of their potent anti-inflammatory effect, corticosteroids have been used alone or in association with antibiotics or other treatments in conditions closely related to COVID-19, including SARS, MERS, severe influenza, community-acquired pneumonia, ARDS, or cytokine release syndrome. However, evidence to support the use of corticosteroids under these conditions is controversial due to various reasons, including the lack of powerful randomised controlled studies, the heterogeneity of the populations studied and the often inappropriate way of recording data on dosages, severity of the disease, and side effects. Based on the mechanism of action and the course of serious viral infections (stage of viral replication followed by immune system's response) it is likely that beneficial effects of corticosteroids in these diseases depend on the timing of treatment, the severity of the clinical condition and the stage of the disease, as well as the dose administered and any individual characteristics of patients. In particular, over the past three years, 3 major randomised clinical trials have suggested a possible benefit of corticosteroids for the treatment of ARDS and septic shock (APROCCHSS studies; ADRENAL; DEXA-ARDS). With regard to use for COVID-19, in the early stages of the epidemic, in the absence of reliable evidence from large-scale randomised clinical trials, there was great uncertainty about the efficacy of corticosteroids in covid-19. Many guidelines on COVID-19 treatment, including those of the WHO, the National Institutes of Health (NIH, USA), the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (ESICM/SCCM) did not initially recommend routine use except for patients who developed

	refractory shock or were treated with corticosteroids prior to diagnosis of COVID-19. For patients with COVID-19 and ARDS who were mechanically ventilated, the ESICM/SCCM guidelines suggested that corticosteroids could be used.
What is the available evidence supporting effectiveness and safety?	***Clinical Studies*** **Studies at 5 October 2020** Data from 5 randomised controlled studies and a meta-analysis conducted by WHO are currently available: *Horby P et al. 2020* (RECOVERY Trial; NCT04381936): The RECOVERY trial (*Randomized Evaluation of Covid-19 Therapy*) is an open label randomised controlled trial conducted in the UK under the coordination of the University of Oxford, which compared different treatments in inpatients with COVID-19. On 16 June 2020 the results of the dexamethasone arm were reported and were published the following month in the *New Engl J Med*. In the period from 19 March to 8 June 2020 6,425 subjects were randomised to receive dexamethasone (n=2,104) or usual therapy (n=4,321). The dose of dexamethasone studied was 6 mg per day, orally or intravenously, for 10 days or until discharge. The primary endpoint of the study was mortality at 28 days. Enrolled subjects had a mean age of 66.1 years (SD +15.7) and 56% had important comorbidities, including diabetes in 24% of subjects, heart disease in 27% and chronic lung disease in 21%. Nearly 90% of the enrolled population had a confirmed diagnosis of SARS-CoV-2 infection. At randomisation 16% were receiving invasive mechanical ventilation or ECMO (extracorporeal oxygenation of the membrane), 60% received only oxygen supplementation (with or without non-invasive ventilation), and 24% did not receive any supplementation. The median duration of treatment was 7 days (IQR, 3-10). With regard to concomitant treatments, approximately 24% of subjects in both arms received azithromycin, while the proportion of subjects receiving hydroxychloroquine, lopinavir/ritonavir, or anti-IL6 was residual and ranged from 0% to 3%. Data analysis showed significantly lower mortality in the dexamethasone arm compared to the control arm (22.9% vs 25.7%; RR 0.83; 95% CI 0.75-0.93; P<0.001). In the pre-specified subgroup analysis, a reduction of the mortality rate in the dexamethasone arm, compared to the control arm, was observed both in the subgroup of subjects with O_2 supplementation (23.3% vs 26.2%; RR 0.82; 95% CI 0.72-0.94) and in that of subjects undergoing invasive mechanical ventilation (29.3% vs 41.4%; RR 0.64; 95% CI 0.51-0.81), while it was not observed in the subgroup of subjects receiving no oxygen supplementation (17.8% vs 14.0%; RR 1.19; 95% IC 0.91-1.55). Overall, the results of the study indicate a clear benefit in terms of mortality with the use of dexamethasone at a dose of 6 mg per day for 10 days in patients with COVID-19 receiving oxygen supplementation, including subjects undergoing invasive mechanical ventilation.

	Main critical issues: • *Absence of specific safety analyses.* *Tomazini BM et al. 2020 (CoDEX RCT; NCT0432740)*: This is a randomised open-label, multicenter, randomised study conducted in Brazil between April and June 2020. The study, initially enhanced to recruit 350 subjects, was terminated early by DSMB which, on 25 June, following the announcement of the above-described RECOVERY study data, did not consider it ethical to continue to enroll patients. The study involved the enrollment of adults with suspected or confirmed infection of SARS-CoV-2, with moderate or severe ARDS (mechanical ventilation or PaO_2:FiO_2<200 mmHg) for no more than 48 hours. Subjects were randomised to receive dexamethasone (20 mg/day IV for the first 5 days and then 10 mg/day IV for 5 days thereafter) or usual care in a 1:1 ratio. The primary endpoint was the number of days free from ventilation during the first 28 days; all-cause mortality at 28 days was the main secondary endpoint. The analysis was conducted on 299 subjects (151 in the dexamethasone arm and 148 in the control arm) with a mean age of 60.1 and of 62.7 years, respectively, in the two study arms. The study population was characterised by severe respiratory impairment (PaO_2:FiO_2<100 in 71.5% of the dexamethasone arm and 73.0% in the control arm) and had important comorbidities, including hypertension (60.3% and 72.3% in the two arms), diabetes (37.8% and 46.6%) and obesity (30.5% and 23.7%). Over 95% of the enrolled population had a confirmed diagnosis of SARS-CoV-2 infection. Concomitant treatments included hydroxychloroquine (23.8% and 18.9% in the two study arms), azithromycin (68.9% and 73.65%), oseltamivir (29.1% and 35.1%). Finally, a significant proportion of subjects (65.6% and 68.2%) were treated with vasopressor agents. The median duration of treatment was 10 days (IQR, 6-10). It should also be noted that in the standard-of-care arm, 52 subjects (35.1%) received at least one dose of corticosteroids during the study. Patients randomised to the dexamethasone group had an average of 6.6 days free from mechanical ventilation versus 4.0 in the standard-of-care group (mean difference, 2.26; 95% CI, 0.2-4.38; P = 0.04). However, there was no significant difference in mortality at 28 days (56.3% vs 61.5%; HR 0.97; 95% CI, 0.72-1.31). At 7 days, however, patients in the dexamethasone group had a significantly better SOFA score (6.1 vs 7.5 P=.004). The incidence of secondary infections was lower in the dexamethasone group (21.9%) compared to control (29.1%), as well as the proportion of serious adverse events (3.3% vs 6.1%), while 47 (31.1%) subjects treated with dexamethasone compared to 42 (28.3%) in the control arm needed insulin therapy to control hyperglycaemia. *Main critical issues:* • *Early break, therefore the study did not reach the estimated sample size.*

	• *The study was not sized to assess a reduction in mortality, since mortality was not a primary outcome.* • *The high proportion of subjects in the control arm who received corticosteroid therapy may have diluted the effect of dexamethasone treatment in the comparison between the two groups.* *Dequin PF et al. 2020 (CAPE COVID Trial; NCT 02517489)*: This is a study incorporated in the Community-Acquired Pneumonia Evaluation of corticosteroids (Capecod) Trial, a large randomised, double-blind study designed to assess the superiority of low-dose hydrocortisone, compared to placebo, in reducing 28-day mortality in patients receiving community-acquired pneumonia intensive care. The study was conducted in France between March and June 2020 and was discontinued following the announcement of data from the RECOVERY study. The study involved the enrollment of adults with suspected or confirmed infection of SARS-CoV-2 with at least one element of severity between: mechanical ventilation, PaO_2/FiO_2<300 mmHg or a pulmonary severity index >130. Subjects were randomised to receive hydrocortisone (200 mg/day IV for the first 7 days, then 100 mg/day IV for 4 days thereafter and 50 mg/day for the last 3 days, with the possibility of using a shortened regimen in responders) or usual care in a 1:1 ratio. The primary endpoint was therapeutic failure defined as death or need for mechanical ventilation or high flow O_2. The study was discontinued after enrolling 149 subjects (76 randomised to the hydrocortisone arm and 73 to the placebo arm). The median age was 62 years and the median duration of symptoms was 9 and 10 days in the two study groups, respectively. The majority of subjects underwent mechanical ventilation (81.6% in the active group and 80.8% in the control group) or high-flow O_2 therapy (13.25 and 12.3%). The 57.9 % and 64.4 % in the active and control groups, respectively, received at least one concomitant treatment including hydroxychloroquine+azithromycin (30.3% and 38.4%), hydroxychloroquine (14.5% and 11.0%), lopinavir/ritonavir (13.2% and 15.1%) and remdesivir (2.6% and 4.1%). In the hydrocortisone group, the proportion of subjects with therapeutic failure at 21 days (primary outcome) was numerically lower, but not statistically significant, compared to the control group (42.1% vs 50.7%; difference -8,6%; 95 % CI 24,9% - 7,7 %; P=.29). There were no significant differences in any of the pre-specified secondary outcomes, in particular, the incidence of secondary infections was comparable in the two groups (37.1% vs 41.1%). No serious adverse events were related to the study treatment. *Main critical issues:* - *Early break, therefore the study did not reach the estimated sample size.* - *Mortality as a single outcome was not included as end-point.*

	- *As a study incorporated in a larger trial, some characteristics specifically useful for covid-19 were not recorded and study groups were not balanced in terms of concomitant treatments.* *REMAP-CAP COVID 19 (NCT 02735707)*. It is one of the domains of the REMAP-CAP platform, an open-label multifactorial adaptive trial platform that allows to study different treatment strategies simultaneously. The study was conducted in Australia, Canada, France, Ireland, Holland, New Zealand, UK and US. Only adult patients with suspected or confirmed infection of SARS-CoV-2 and with severe disease, hospitalized in the intensive care unit for respiratory (mechanical ventilation or high-flow oxygen) or cardiac (infusion of vasopressors or inotropics) support were enrolled in the domain related to corticosteroid therapy. Subjects enrolled were randomised to one of the following treatments: fixed-dose hydrocortisone (50 mg IV every 6 hour for 7 days), shock-dependent hydrocortisone (50 mg IV every 6 hour for the duration of the shock phase up to a maximum of 28 days), and standard treatment. The primary endpoint was the number of days without any respiratory or cardiac support. The statistical analysis included a Bayesian logistic model and was conducted on 576 participants, 379 were randomised within the corticosteroid domain and 101 to the control arm. The median age ranged from 59.5 to 60.4 years. Most patients received invasive mechanical ventilation (range 50.0 %-63.5 %) or non-invasive (range 24.1 %-33.6 %). It should be noted that approximately 15% of subjects in the control arm were then administered corticosteroids during the study. The median number of days without support was 0 (IQR, –1 to 15), 0 (IQR, –1 to 13) and 0 (IQR, –1 to 11) for the fixed-dose hydrocortisone group, shock-dependent hydrocortisone group, and control group, respectively. Compared to the latter, the adjusted OR was 1.43 (95% CI, 0.91-2.27) for the fixed dose and 1.22 (95% CI, 0.76-1.94) for the shock-dependent dose, with a retrospective likelihood of 93 % and 80 %, respectively. Intrahospital mortality rates were 30% (n = 41/137), 26% (n = 37/141) and 33% (n = 33/99) respectively in the fixed dose group (OR 1.03; 95% CI, 0.53-1.95), at shock-dependent doses (1.10; 95% CI, 0.58-2.11) and without hydrocortisone. Serious adverse events were reported in 4 (3%), 5 (3%) and 1 (1%) patients in the three study groups. *Main critical issues:* - *Early break, therefore the study did not reach the estimated sample size to evaluate the primary outcome and secondary outcomes.* - *A small proportion of subjects in the control arm received corticosteroid therapy, which may have diluted the effect of active treatment in the comparison between the two groups.*

	Jeronimo CMP et al. 2020 (METCOVID Study; NCT 04343729). This is a small randomised, double-blind, phase IIb study conducted in a single center in Manaus (Western Brazilian Amazon); Brazil. The study enrolled adult subjects with confirmed or suspected diagnosis of covid-19 and SpO2 ≤ 94 % in ambient air or who have undergone additional oxygen therapy. The enlisted subjects were assigned to receive methylprednisolone intravenously (0.5 mg/kg), twice daily for 5 days or placebo (salt solution), in a 1:1 ratio. As per hospital protocol, all patients with the ARDS criteria used endovenous ceftriaxone (1g 2x for 7 days) plus azithromycin (500mg 1x for 5 days) or clarithromycin (500mg 2x for 7 days). The primary endpoint was mortality at 28 days. The study was enhanced by estimating the death rate at 50% in the control arm and assuming a 50% reduction in mortality. Between April and June 2020, 416 subjects were randomised, with a mean age of 55 years. As regards comorbidities, 49% had hypertension, 29% diabetes and a large proportion of subjects abused alcohol (27%). The 33.8% of enrolled subjects underwent invasive mechanical ventilation and 36% were admitted to ICU. The average time between diagnosis and randomisation was 13 days. Overall mortality at 28 days was 37.1% (72/194) in the methylprednisolone vs 38.2% (76/199) group in the placebo group (P=0.629), while reduced mortality in the steroid group was observed in a post-hoc analysis including patients over 60 years of age (46.6% vs 61.9%); HR 0.634; 95% CI 0.411-0.978). *The study is not directly comparable with the trials previously exposed and presents some critical issues:* - *Small monocentric study.* - *Doubts about the appropriateness of sample size estimation.* - *The more advanced study population and the use of a different corticosteroid for a shorter period make the results difficult to compare with those of the other available studies and thus make it difficult to interpret them in the context of current scientific knowledge.* The *WHO Rapid Evidence Appraisal for Covid-19 Therapies (REACT) Working Group* recently completed a meta-analysis to estimate the efficacy of corticosteroid administration, compared to standard of care, in covid-19 inpatients in critical conditions. The meta-analysis included 7 trials: in addition to 4 of the studies described above (RECOVERY, Codex, CAPE Covid, REMAP-CAP COVID-19; while the METACOV study was not yet available), the authors received data from other 3 clinical trials identified after careful review of the main, but not yet published, databases (DEXA-COVID study, conducted in subjects undergoing invasive mechanical ventilation, the Steroids-SARI study carried out in patients receiving intensive care and the covid-Steroid study, which included subjects with oxygen supplementation of >10L/min). The risk of bias was assessed as “low” in 6 of the 7 studies examined. The analysis was conducted on a total

	of 1,703 patients (29% women, median age: 60 years, range: 52-68 years). Among the 678 patients randomised to receive corticosteroids there were 222 deaths, while among 1,025 patients randomised to receive standard therapy there were 425 deaths (OR 0.66; 95% IC 0.53-0.82; P<0.001), which corresponds to an absolute mortality risk of 32% with corticosteroids compared to 40% with standard care. Following publication of the METCOVID study, the authors repeated their primary analysis with similar results (OR 0.66. 95% CI 0.54-0.82). By assessing the different corticosteroids studied the OR was 0.64 (95% CI 0.50-0.82; P< 0.001) for dexamethasone (3 studies, 1,282 patients and 527 deaths), 0.69 (95 % CI, 0,43-1,12; P = 0,13) for hydrocortisone (3 studies, 374 patients, and 94 deaths) and at 0,91 (95 % CI, 0,29-2,87; P = 0.87) for methylprednisolone (1 study, 47 patients and 26 deaths). No major differences were recorded in the analysis of data stratified by either high or low corticosteroid dose. Among the 6 trials that reported serious adverse events, there were 64 events among the 354 randomised corticosteroids patients and 80 events among the 342 randomised patients in the control arm. Overall, the evidence analysed shows a protective effect of corticosteroid use on mortality in subjects with severe COVID-19 disease undergoing oxygen supplementation with and without mechanical ventilation. Although the most significant results were achieved with dexamethasone, the clinical benefit is also evident in terms of numbers with other substances, suggesting an overall class effect.
Which patients are corticosteroids recommended?	***Therapeutic use*** Use of corticosteroids is recommended in inpatients with severe COVID-19 disease who require oxygen supplementation, with or without mechanical ventilation (invasive or non-invasive). Based on current literature, the use of corticosteroids should be considered as a standard of care in this population as it is the only treatment that has shown a benefit in terms of reducing mortality. Regarding the type of corticosteroid, although the most robust evidence was obtained with dexamethasone, a class effect is hypothesised.
What are the recommendations of international bodies?	**EMA** On 18 September 2020 EMA became aware of the conclusion of a review procedure, under Art.5 (3) of Regulation 726/2004, of the available evidence on the use of dexamethasone for the treatment of COVID-19. Based on the review of available data, the EMA has approved the use of dexamethasone in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who require additional oxygen therapy (both classic oxygen therapy and mechanical ventilation). Dexamethasone can be taken by mouth, or by injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 mg once a day for up to 10 days.

	WHO (Living Guidance, 02 September 2020). The use of systemic corticosteroids is recommended in patients with severe or critical COVID-19 disease (strong recommendation with moderate strength of evidence). Its use is not recommended in non-severe COVID-19 cases (conditional recommendation, with low evidence strength). **Infectious Diseases Society of America Guidelines (IDSA**) [updated 25/6/20]. The Panel recommends the use of systemic corticosteroids in patients with severe COVID-19 disease (conditional recommendation with moderate evidence). Dexamethasone (6 mg IV or PO for 10 days or until discharge if prior) or equivalent glucocorticoid (e.g. methylprednisolone 32 mg and prednisone 40 mg) is recommended. The Panel suggests that corticosteroids should not be used in inpatients with COVID-19 without hypoxaemia and therefore who not require additional oxygen (conditional recommendation, with a low strength of evidence). **NIH – US CDC** Based on the data from RECOVERY study, the COVID-19 Treatment Guidelines recommended that dexamethasone 6 mg per day should be used for up to 10 days or until discharge (if prior), for the treatment of COVID-19 in mechanically ventilated inpatients (AI) as well as in inpatients who require additional oxygen but are not mechanically ventilated (BI). The Panel recommends that dexamethasone should not be used for the treatment of COVID-19 in patients who do not require additional oxygen (AI). Should dexamethasone be unavailable, the Panel recommends the use of alternative glucocorticoids such as prednisone, methylprednisolone or hydrocortisone (AIII).
At what doses are corticosteroids preferably prescribed and in which forms?	**Recommended dose** As indicated by the CHMP, the recommended dose for dexamethasone in adults and adolescents is 6 mg once daily for up to 10 days. Dexamethasone can be taken by mouth, or by injection or infusion (drip) into a vein. Any other corticosteroids should be used at equivalent doses, in particular the IDSA guideline and the AR-CHMP suggests: • methylprednisolone 32 mg • prednisone: 40 mg • hydrocortisone: 160 mg
Who is expected to prescribe corticosteroids during the emergency phases of the COVID-19 pandemic?	**Prescription procedure** Prescription of corticosteroids for their authorised uses is not restricted.

What are major risks in terms of adverse reactions?	**Cautions** The decision to start corticosteroid therapy should be based on careful consideration of the benefit/risk profile in individual patients, including careful monitoring of any adverse events. In general corticosteroids should be used with caution in the presence of: non-specific ulcerative colitis at high risk for perforation; abscesses or other pyogenic infections; diverticulitis; recent intestinal anastomosis; active or latent forms of peptic ulcer; renal impairment; hypertension; osteoporosis; myasthenia gravis; glaucoma. For a full review, please refer to the data sheets.
Can it be co-administered with other treatments?	**Main interactions** Dexamethasone is a moderate inducer of CYP 3A4. Co-administration with other medicinal products metabolised by CYP 3A4 may increase their clearance, resulting in decreased plasma concentrations. **It is recalled that concomitant administration of remdesivir and corticosteroids has not been formally studied.** For a complete examination please refer to the respective technical data sheets. For further information on interactions, please visit: https://www.covid19-druginteractions.org/
Ongoing trial in Italy	Please refer to the following page of the AIFA website: https://www.aifa.gov.it/sperimentazioni-cliniche-covid-19
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