Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Drug reaction with eosinophilia and systemic symptoms (DRESS) in patients with COVID-19

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To the Editor,

Critically ill, hospitalized patients with coronavirus disease 2019 (COVID-19) are treated with multidrug regimens combining immunomodulation with antiviral agents to prevent progressive respiratory failure. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug-induced systemic hypersensitivity reaction potentially favoured by viral triggers in a permissive genetic background [1–3], thus potentially complicating the course of hospitalized patients with COVID-19.

We retrospectively reviewed the clinical data of patients with COVID-19 admitted to San Raffaele Hospital, Milan, Italy during the first three contagion waves (24th February to 22nd May 2020, 1st September to 31st December 2020, and 1st January to 31st March 2021) and enrolled in the COVID-BioB protocol (NCT04318366). Treatment protocols changed significantly across the three timeframes, following changing paradigms in the literature [4]: hydroxychloroquine and lopinavir/ritonavir were largely employed until May 2020 and avoided thereafter, while the opposite scenario was observed for corticosteroids; antibiotics were also probably prescribed more appropriately after the first pandemic wave [5]. We classified patients with DRESS according to the RegiSCAR algorithm [4]. Treatment for <3 months but >3 days or discontinuation within 14 days from skin rash (temporal criterion 1) and previous evidence of potential involvement from literature (causality criterion 2) were used to rank culprit drugs as improbably (not meeting 1), possibly (meeting 1 but not 2) or probably involved (meeting 1 and 2) [2]. The incidence rate of DRESS in patients with COVID-19 was calculated using the following formula:

$$Inc_{rate} = \frac{total\ DRESS\ cases}{hospitalized\ patients} \times \frac{1}{months}$$

and compared to the incidence rate of DRESS cases among non-COVID-19 patients hospitalized in the same Institution between January 2017 and December 2019. Potential culprit drugs in non-COVID-19 patients were also recorded.

Among 986 COVID-19 patients admitted during the first wave (February to May 2020) we identified five cases of DRESS (two females, three males; age 40–74 years; Table 1). The incidence rate of DRESS among COVID-19 patients in this timeframe was 0.17/100 patient-months. By contrast, no DRESS cases were found among 1010 patients with COVID-19 during the second wave (September to December 2020) or among 725 patients with COVID-19 during the third wave (January to March 2021). The incidence rate of DRESS among non-COVID-19 patients hospitalized in the preceding 3 years was 0.0005/100 patient-months. Due to respiratory insufficiency, all five patients with COVID-19 and DRESS required non-invasive mechanical ventilation and three were admitted to the intensive care unit. One patient died due to a secondary infection. DRESS occurred 10–30 days from hospital admission, 14–37 days from COVID-19 onset and 8–22 days from initiation of suspected

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Table 1
Clinical features of patients with eosinophilia and systemic symptoms (DRESS) and coronavirus disease 2019 (COVID-19)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics and clinical presentation					
Sex	Female	Male	Male	Female	Male
Age (years)	56	67	74	69	40
Comorbidities	Hypertension, diabetes, severe obesity, severe depression and anxiety, gastritis	None	Hypertension, atrioventricular block II degree Mobitz I	Hypertension	Hypertension
Known allergies	Acetylsalicylic acid	None	None	None	None
Time from COVID-19 onset to admission (days)	7	4	8	1	4
COVID-19 symptoms	Fever, dyspnoea	Fatigue, myalgia, cough, fever	Cough, dyspnoea, fever	Dyspnoea, cough	Fever, dyspnoea, cough, loss of appetite, diarrhoea
Pneumonia	Yes	Yes	Yes	Yes	Yes
Not invasive mechanical ventilation	Yes	Yes	Yes	Yes	Yes
Admission to Intensive Care Unit	No	Yes	Yes	No	Yes
SARS-CoV-2-positive swab (days from admission)	0	−10	0	0	0
Outcome	Discharged (day 40)	Discharged (day 93)	Deceased (by sepsis, day 33)	Discharged (day 41)	Discharged (day 27)
Features of DRESS syndrome					
RegiSCAR validation criteria (score) [4]	6 (definite)	5 (probable)	5 (probable)	5 (probable)	5 (probable)
Skin rash					
Extension (skin surface %)	90	72	72	54	83
Appearance	Maculopapular	Maculopapular	Maculopapular	Maculopapular	Maculopapular
Onset (days from admission)	30	17	17	22	10
Onset (days from probable suspected drug initiation)	20 (piperacillin/tazobactam) 20 (vancomycin)	17 (hydroxychloroquine); 9 (piperacillin/tazobactam)	17 (hydroxychloroquine); 9 (vancomycin)	22 (hydroxychloroquine); 8 (piperacillin/tazobactam)	9 (hydroxychloroquine) 9 (ceftriaxone)
Eosinophilia					
Peak (cells/μL)	5300	2000	5300	2300	2400
Onset (days from admission)	14	16	14	18	23
Onset (days from probable suspected drug initiation)	4 (piperacillin/tazobactam); 4 (vancomycin)	16 (hydroxychloroquine); 8 (piperacillin/tazobactam)	14 (hydroxychloroquine); 6 (vancomycin)	18 (hydroxychloroquine); 4 (piperacillin/tazobactam)	22 (hydroxychloroquine); 22 (ceftriaxone)
Fever (>38.5°C)	Yes	No	Yes	No	Yes
Involved organs	Liver, kidney	Liver, kidney	Heart	Liver	Kidney
Potential culprit drugs[a]					
Likely	Piperacillin/tazobactam, vancomycin	Hydroxychloroquine, piperacillin/tazobactam	Hydroxychloroquine, vancomycin	Hydroxychloroquine, piperacillin/tazobactam	Hydroxychloroquine, ceftriaxone
Possible	Fluvoxamine, promazine, haloperidol, iopamidol	Lopinavir/ritonavir, anakinra, propofol, fentanyl, midazolam, cisatracurium, linezolid, vitamin B1, iopromide	Levofloxacin, iopamidol	Lopinavir/ritonavir, sarilumab, iopamidol	Lopinavir/ritonavir, azithromycin, oseltamivir, anakinra, ethacrynic acid
Unlikely	Lopinavir/ritonavir, lorazepam, hydroxychloroquine, levofloxacin, furosemide, enoxaparin, methylprednisolone, hydroxyzine	Omeprazole, ceftriaxone, furosemide, enoxaparin, quetiapine, norepinephrine, alprostadil, ethacrynic acid, labetalol, clonidine, acetazolamide, fluvoxamine, prednisone, hydroxyzine, tigecyclin, daptomycin	Azithromycin, propofol, remifentanyl, rocuronium, fluconazole, paracetamol, furosemide, Canrenone, Enoxaparin, Clorfenamine, omeprazole, clonazepam, norepinephrine, tigecyclin, daptomycin	Omeprazole, furosemide, enoxaparin, levofloxacin, spironolactone, prednisone, hydroxyzine	Furosemide, nebivolol, omeprazole, propofol, fentanyl, midazolam, cisatracurium, norepinephrine, enoxaparin, human albumin, meropenem, linezolid, celecoxib, prednisone, hydroxyzine, daptomycin
Virological studies (DNA/RNA)	HBV, HCV (negative)	HBV, HCV, EBV, CMV (negative)	HBV, HCV (negative)	HBV, HCV (negative)	HBV, HCV (negative)
Time to DRESS resolution (days)	26	29	NA (death at day 19 from DRESS onset)	36	22

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a] Treatment for <3 months but >3 days or discontinuation within 14 days from skin rash (temporal criterion 1) and previous evidence of potential involvement from available literature (causality criterion 2), were used to rank culprit drugs as improbably (not meeting 1), possibly (meeting 1 but not 2) or probably involved (meeting 1 and 2) [4].

culprit medications. Maculopapular rash and peripheral-blood eosinophilia were observed in all patients (Supplementary Material Fig. S1). All patients had a rise in body temperature after initial defervescence, with three patients exceeding 38.5°C. Liver, kidney, and heart involvement occurred in three, three, and one patients each. Hydroxychloroquine and/or β-lactams were deemed probably involved drugs in all patients. No patch or intradermal tests were performed to further prove drug causality, which constitutes a limitation of our study. Consistently with the literature, β-lactams, along with vancomycin and anticonvulsants, were the most frequent culprit drugs in our historical DRESS cohort (Supplementary Material Table S1) [1,2]. In COVID-19 patients, DRESS resolved 22–36 days after discontinuation of putative culprit drugs and supportive therapy with corticosteroids and antihistamines (Table 1).

Our observations suggest that DRESS might complicate the course of hospitalized COVID-19 patients treated with multiple therapies. Since no DRESS cases were found during the latter two pandemic waves, while DRESS incidence during the first one was even higher than in the pre-pandemic setting, a differential use of selected drugs across the three waves (namely hydroxychloroquine, lopinavir/ritonavir and possibly β-lactams) might account for at least part of the drug hypersensitivity risk in patients with COVID-19. Furthermore, the use of corticosteroids during the second and third waves might have hampered both hypersensitivity mechanisms leading to DRESS and SARS-CoV-2-related inflammatory stimuli. Consistently, in our series, a clinical diagnosis of DRESS was supported by a combination of concomitant hallmark features that were temporarily uncoupled from the COVID-19 course yet related to established DRESS triggers, including (a) non-septic fever after initial defervescence, (b) high-grade eosinophilia, as opposed to the typical COVID-19-related eosinopenia, (c) typical, extensive maculopapular rash, and (d) organ damage. However, conventional clinical tools used to recognise DRESS—such as the RegiSCAR algorithm—may pose several challenges to allergists in the context of COVID-19, as isolated items of the score might overlap with clinical manifestations of SARS-CoV-2 infection. Awareness of DRESS in the context of COVID-19 and prompt withdrawal of culprit medication(s) in established cases might be crucial in limiting COVID-19-related morbidity. In the unprecedented clinical and pharmacological setting of COVID-19, new or less described associations between potential offending drugs and DRESS should not be overlooked.

Author contributions

GAR, EDT, LD and MRY designed the work and acquired, analysed and interpreted the data. GAR and EDT drafted the manuscript. MT, PS, and FC contributed to data acquisition and interpretation. All authors revised the work critically for important intellectual content and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GAR and EDT contributed equally as first authors, LD and MRY as senior authors.

Transparency declaration

The authors declare that they have no conflict of interest in connection with this work. No specific funding was received for this study.

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Appendix A. Supplementary data

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