1 **Title: Management of patients with atopic dermatitis undergoing systemic therapy during**
2 **COVID-19 pandemic in Italy: data from the DA-COVID-19 registry**
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4 **Running title:** AD management during COVID-19 pandemic
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6 **Authors:**
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8 Andrea **Chiricozzi**[1,2,*,§],**MD,** Marina **Talamonti**[3,§], **MD,** Clara **De Simone**[1,2], **MD,** Marco **Galluzzo**[3,§],
9 **MD,** Niccolò **Gori**[1,2], **MD,** Gabriella **Fabbrocini**[4], **MD,** Angelo Valerio **Marzano**[5,6], **MD,** Giampiero
10 **Girolomoni**[7], **MD,** Annamaria **Offidani**[8], **MD,** Maria Teresa **Rossi**[9], **MD,** Luca **Bianchi**[3], **MD,** Antonio
11 **Cristaudo**[10], **MD,** Maria Teresa **Fierro**[11], **MD,** Luca **Stingeni**[12], **MD,** Giovanni **Pellacani**[13], **MD,**
12 Giuseppe **Argenziano**[14], **MD,** Annalisa **Patrizi**[15], **MD,** Paolo **Pigatto**[16], **MD,** Marco **Romanelli**[17], **MD,**
13 Paola **Savoia**[18], **MD,** Pietro **Rubegni**[19], **MD,** Caterina **Foti**[20], **MD,** Nicola **Milanesi**[21], **MD,** Anna
14 **Belloni Fortina**[22], **MD,** Maria Rita **Bongiorno**[23], **MD,** Teresa **Grieco**[24], **MD,** Sergio **Di Nuzzo**[25], **MD,**
15 Maria Concetta **Fargnoli**[26], **MD,** Andrea **Carugno**[27], **MD,** Alberico **Motolese**[28], **MD,** Franco
16 **Rongioletti**[29], **MD,** Paolo **Amerio**[30], **MD,** Riccardo **Balestri**[31], **MD,** Concetta **Potenza**[32], **MD,**
17 Giuseppe **Micali**[33], **MD,** Cataldo **Patruno**[34], **MD,** Iris **Zalaudek**[35], **MD,** Maurizio **Lombardo**[36], **MD,**
18 Claudio **Feliciani**[25], **MD,** Fabrizio **Guarneri**[37], **MD,** Ketty **Peris,**[1,2] **MD; DA-COVID-19 study group.**
19
20
21 **Affiliations**
22

23 [1] Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario
24 A. Gemelli IRCCS, Rome, Italy.
25 [2] Dermatologia, Università Cattolica del Sacro Cuore, Rome, Italy.
26 [3] Dermatology Unit, Policlinico Tor Vergata, Department of Systems Medicine, Tor Vergata
27 University of Rome, Italy
28 [4] Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples
29 Federico II, Naples, Italy.
30 [5] Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
31 [6] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan,
32 Italy.
33 [7] Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona,
34 Italy.
35 [8] Dermatological Clinic, Department of Clinical and Molecular Sciences, Polytechnic University of
36 the Marche Region, Ancona, Italy.
37 [9] Department of Dermatology, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy.
38 [10] Clinical Dermatology, San Gallicano Dermatological Institute, Rome, Italy.
39 [11] Medical Sciences Department, Dermatologic Clinic, University of Turin, Turin, Italy.
40 [12] Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy.
41 [13] Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy.
42 [14] Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy.
43 [15] Dermatology UOC, Department of Experimental, Diagnostic and Specialty Medicine, University of
44 Bologna, Italy.
45 [16] Department of Biomedical, Surgical and Dental Sciences, Clinical Dermatology, IRCCS Galeazzi
46 Orthopaedic Institute, University of Milan, Milan, Italy.
47 [17] Department of Dermatology, University of Pisa, Pisa, Italy.
48 [18] Department of Health Sciences, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy.

49 [19] Dermatology Unit, Department of Medical, Surgical and Neurosciences, University of Siena, Italy.

50 [20] Department of Biomedical Science and Human Oncology, Unit of Dermatology, University of
51 Bari, Bari, Italy.

52 [21] Dermatology Clinic, Department of Health Sciences, University of Florence, Florence, Italy.

53 [22] Dermatology Unit - Department of Medicine DIMED, University of Padova, Padova, Italy

54 [23] Section of Dermatology, Department of Health Promotion, Mother and Child Care, Internal
55 Medicine and Medical Specialties, University of Palermo, Palermo, Italy.

56 [24] Unit of Dermatology, Department of Clinical Internal, Anesthesiological and Cardiovascular
57 Sciences, Sapienza University of Rome, Rome, Italy.

58 [25] Department of Medicine and Surgery, Section of Dermatology, University of Parma, Parma, Italy.

59 [26] Dermatology, Department of Biotechnological and Applied Clinical Sciences, University of
60 L'Aquila, L'Aquila, Italy.

61 [27] Dermatology Unit, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy.

62 [28] Dermatology Unit, Department of Medical Specialties, Arcispedale Santa Maria Nuova-IRCCS di
63 Reggio Emilia, Reggio Emilia, Italy.

64 [29] Section of Dermatology, Department of Medical Sciences and Public Health, University of
65 Cagliari, Cagliari, Italy.

66 [30] Department of Medicine and Aging Science, Dermatologic Clinic, G. D'Annunzio University,
67 Chieti, Italy.

68 [31] Division of Dermatology, Santa Chiara Hospital, Trento, Italy.

69 [32] Department of Medico-Surgical Sciences and Biotechnologies, Dermatology Unit 'Daniele
70 Innocenzi' Sapienza University of Rome - Polo Pontino, Rome, Italy.

71 [33] Dermatology Clinic, University of Catania, Catania, Italy.

72 [34] Dermatology Unit, Department of Health Sciences, Università Magna Graecia, Catanzaro, Italy.

73 [35] Department of Dermatology, University of Trieste, Trieste, Italy.

74 [36] Unit of Dermatological Diseases, ASST Sette Laghi, Ospedale di Circolo, Varese, Italy.

75 [37] Dermatology, Department of Clinical and Experimental Medicine, University of Messina,
76 Messina, Italy.

77 [38] Allergology, ASL Modena, Italy

78

79 **DA-COVID-19 Study Group**
80 Giacomo **Caldarola**[1], Dionisio **Silvaggio**[3]**,** Maddalena **Napolitano**[4], Silvia Mariel **Ferrucci**[5]**,** Giacomo
81 **Dal Bello**[7], Tommaso **Bianchelli**[8], Chiara **Rovati**[9], Flavia **Pigliacelli**[10], Michela **Ortoncelli**[11], Katharina
82 **Hansel**[12], Giulia **Calabrese**[14], Camilla **Loi**[15], Michela **Iannone**[17], Federica **Veronese**[18], Paolo **Romita**[20],
83 Greta **Tronconi**[21], Francesca **Caroppo**[22], Giovanna **Tilotta**[23], Alvise **Sernicola**[24], Maria **Esposito**[26]**,**
84 Francesca **Raponi**[27]**,** Viviana **Piras**[29], Giulio **Gualdi**[30], Giulia **Rech**[31], Maria Letizia **Musumeci**[33], Steven
85 Paul **Nisticò**[34]**,** Alessio **Campitiello**[37]**,** Laura **Bonzano**[38]

86

87

88 [§] **These authors contributed equally to this work**

89

90 ***Corresponding author**
91 Andrea Chiricozzi, MD
92 Institute of Dermatology
93 Catholic University of the Sacred Heart – Policlinico Universitario A. Gemelli IRCCS Foundation,
94 Rome
95 Largo Agostino Gemelli 8, 00168 Rome, Italy
96 Tel.: +39-339.5668320

97 Fax: +39-0761-571321
98 Email: chiricozziandrea@gmail.com
99
100

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Abstract

Background: Few and small studies have described the management of immunomodulant/immunosuppressive therapies or phototherapy in atopic dermatitis (AD) patients during coronavirus disease 2019 (COVID-19) pandemic.

Methods: A national registry, named DA-COVID-19 and involving 35 Italian dermatology units, was established in order to evaluate the impact of COVID-19 pandemic on the management of adult AD patients treated with systemic immunomodulant/immunosuppressive medications or phototherapy. Demographic and clinical data were obtained at different timepoints by teledermatology during COVID-19 pandemic, when regular visits were not allowed due to sanitary restrictions. Disease severity was assessed by both physician- and patient-reported assessment scores evaluating itch intensity, sleep disturbances, and AD severity.

Results: A total of 1831 patients were included, with 1580/1831 (86.3%) continuing therapy during pandemic. Most patients were treated with dupilumab (86.1%, 1576/1831) that was interrupted in only 9.9% (156/1576) of cases, while systemic immunosuppressive compounds were more frequently withdrawn. Treatment interruption was due to decision of the patient, general practitioner or dermatologist in 39.9% (114/286), 5.6% (16/286), and 30.1% (86/286) of cases, respectively. Fear of increased susceptibility to SARS-CoV-2 infection (24.8%, 71/286) was one of the main causes of interruption. Sixteen patients (0.9%) resulted positive to SARS-CoV-2 infection, 3 of them (0.2%) were hospitalized but no cases of COVID-related death occurred.

Conclusions: Most AD patients continued systemic treatments during COVID pandemic and lockdown period, without high impact on disease control, particularly dupilumab-treated patients.

Keywords: Atopic Dermatitis; COVID; SARS-CoV

Introduction

COVID-19, caused by SARS-CoV-2 infection has spread rapidly worldwide becoming pandemic, as defined by the World Health Organization on March 11th 2020.[1] Most patients exhibit mild-to-moderate symptoms and recover without sequelae, though hospitalization, generally due to pneumonia, and more severe respiratory involvement such as acute respiratory distress syndrome, septic shock, and/or multiple organ failure, associated with high mortality, may occur.[1] Italy has faced the first wave of SARS-CoV-2 infection out of China before the rapid worldwide pandemic spreading. To face the virus spreading, a nationwide lockdown period (phase I) limiting all kind of activities including health care services, was decided on March 10th and lasted until May 4th, when a phase II was planned with a gradual re-opening of hospital dermatology services. During these two initial phases, medical visits were restricted to urgent cases, and the use of teledermatology was implemented in many dermatological services. On June 15th, 2020, a phase III was established recovering almost all activities with sanitary restrictions, and health care services were restored based on the decision of local sanitary authorities.

Thereby, COVID-19 pandemic led to the sudden need of increasing the use of web- and phone-consulting, and defining practical guidelines for the management of immune-mediated dermatologic conditions, such as AD that in moderate-to-severe cases are commonly treated with systemic immunomodulant/immunosuppressive compounds or phototherapy. The effect of immunomodulant/immunosuppressive compounds on the clinical course of COVID-19 is currently unclear and there is concern of an increased risk of infection in these patients, though the continuation of therapy during pandemic was recommended by national and international scientific societies.[2-6] Nevertheless, immunomodulant/immunosuppressive agents, such as methotrexate, mycophenolate, azathioprine, and cyclosporine were suggested to be tapered to the lowest effective dose, likely avoiding disease flare, and to consider drug discontinuation in

215   patients when viral symptoms are present.[2,5] Similarly, caution was recommended in prescribing

216   systemic corticosteroids given their broad immunosuppressive effects.[2,5] Furthermore, some

217   authors recommended halting office-based phototherapy to minimize potential exposure to SARS-

218   CoV-2 virus and instead encourage exposure of affected areas to natural sunlight, bleach baths,

219   and wet wraps.[5] Beside immunosuppressive systemic compounds, dupilumab, an anti-IL-4/IL-13

220   biologic agent, showed similar infection rates compared to placebo during the phase 3 trials.[7]

221   However, current recommendations are based on limited knowledge regarding the risk of

222   systemic immunomodulant/immunosuppressive compound use, and few data related to AD

223   patients treated during COVID-19 pandemic.

224   We designed a national registry, the DA-COVID-19 registry, aimed to evaluate the impact of the

225   pandemic on the therapeutic management and clinical course of AD in patients treated with any

226   systemic immunomodulant/immunosuppressive compound or phototherapy. This observational

227   study analyzed clinical and demographic characteristics of moderate-to-severe AD patients, who

228   were managed with telemedicine and eventually by regular ambulatory visits during the COVID-19

229   pandemic.

Methods

This cross-sectional, multicentric, observational study was conducted in 35 Italian centers. This registry, which was aimed to collect data on moderate-severe AD patients treated with systemic agents and/or phototherapy during COVID-19 outbreak, has been promoted by the Italian Society of Dermatology (SIDeMaST) and approved by the national ethical committee for COVID-19-related studies (Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani I.R.C.C.S.). The study period included the three phases of first wave COVID-19 pandemic in Italy (Figure 1).

Adult patients (aged ≥ 18 years) affected by moderate-to-severe AD, treated with systemic immunosuppressive/immunomodulant compounds or phototherapy, were included in the DA-COVID-19 registry if face-to-face evaluation or remote visit (via telephone- or web-consulting) were performed between March 10th and April 30th, 2020. By April 30th, data have been collected monthly, thereafter, on an ad-hoc database. Data were collected at 3 different timepoints: April 30th (Timepoint 1), May 30th (Timepoint 2), and June 30th (Timepoint 3) (Figure 1). Subjects who signed the informed consent were included in this study. Baseline data included age, gender, occupation, atopic comorbidities, smoking habits (smoker, former smoker, or non-smoker), and disease severity.

Disease severity assessment

Disease severity was assessed by EASI score at timepoint 1 (either assessed during face-to-face visit or the last recorded EASI score in patient's file) and at timepoint 3, being performed if dermatology units restored their regular outpatient clinical activity. At timepoint 2, due to sanitary restriction, no EASI score was reported. In addition, patient-reported evaluations included: 0-10 NRS for pruritus intensity (itch-NRS), sleep disturbances/sleeplessness by a 0-10 NRS scale (sleep-

254 NRS), self-evaluated AD severity by a 0-10 NRS scale (AD-NRS), self-evaluation of patient's disease

255 course (patient perception of "AD status", defined as stable/no flaring, improved, or worsened,

256 during the observation period), and ongoing treatment. Details about treatment interruption or

257 suspension were recorded. Data on SARS-CoV-2 swab testing, hospitalization, clinical outcomes of

258 COVID-19 disease, and quarantine due to close contact to COVID-9 patients were also collected.

259

260 *Statistical analysis*

261 Patients were analyzed according to their ongoing therapy to identify possible differences in any of

262 the demographic or clinical variables collected. Frequency and percentages were the descriptive

263 analyses performed on the categorical variables. Continuous variables were summarized as means

264 ± standard deviation. For categorical variables, differences between groups were evaluated using

265 Chi-square test or Fisher's exact test (if more than 20% of the cells in a contingency table have

266 expected counts less than 5). For quantitative variables, the Shapiro-Wilk test was performed in

267 order to test the normality of data. If the p-value was less than or equal to 0.05 (non-normality),

268 the comparison between groups was performed by means of the non-parametric Wilcoxon rank

269 sum test. Otherwise, the comparison was performed using the T test. Moreover, comparison

270 between timepoint 1 value and the other timepoints was performed using the paired t-test (or the

271 Wilcoxon signed rank test in the case of non-normal data). Finally, an ANOVA test (or Kruskal–

272 Wallis test in the case of non-normal data) was performed to compare the means in case of more

273 than 2 groups. Differences were considered statistically different if p values resulted <0.05.

274 Analyses were performed using software SAS 9.4 version (SAS, NC, USA).

Results

The DA-COVID registry included 1831 patients with moderate-to-severe AD presenting demographic and clinical characteristics as illustrated in Table 1. Overall, 142/1831 (7.7%) patients were lost to follow-up throughout the observation period.

SARS-CoV-2 infection in the study population

Seventy-nine of 1831 (4.3%) AD patients performed SARS-CoV-2 nasal-throat swab testing; 16/1831 (0.9%) had a confirmed diagnosis of SARS-CoV-2 infection and 3 (0.2%) were hospitalized. No cases of death from COVID-related disease occurred in our study population throughout the whole observation period. The 16 SARS-CoV-2 positive patients had a mean age of 45.1 years (±16.4), 9 were females (56.3%), presenting rhinitis as the most common atopic comorbidity 10/16 (62.5%) (Table S1). AD severity was in line with the overall patient population (data not shown). Fifteen of 16 (93.8%) patients were undergoing dupilumab therapy when SARS-CoV-2 occurred (Table S1). Half of SARS-CoV-2 positive patients discontinued treatment. SARS-CoV-2 positive patients who continued treatment were all undergoing dupilumab therapy. No COVID-19 complication or worsening was reported in those cases continuing therapy. Because of close contact with COVID-19 cases or high-risk conditions for SARS-CoV-2 infection, 3.2% (58/1831) of patients underwent quarantine.

Characterization of treatment path in the study population

Overall, 63.2% (1157/1831) and 36.8% (674/1831) of patients were treated in monotherapy or with two or more systemic agents, respectively. Most patients were treated with dupilumab (86.1%, 1576/1831 patients): 64.3% of them (1013/1576) with dupilumab monotherapy, while in 35.7% (563/1576) dupilumab was used together with other systemic agents or phototherapy (Figure S1). Notably, patients treated with dupilumab combined with other systemic therapies had

299 significantly higher rates of concomitant atopic conditions compared to patients treated with

300 dupilumab monotherapy or systemic immunosuppressive compounds (p<0.001; Table S2).

301 Immunosuppressive systemic compounds were used as either monotherapy or combination

302 therapy as showed in Table 2.

303 In a small proportion of patients (53/1831, 2.9%), systemic therapy was modified including a total

304 of 66 therapy modifications consisting of drug dosage adjustment (i.e., tapering down or

305 increasing dose) or lengthening drug administration interval, at least once. The addition to or

306 substitution of the systemic therapy with topical agents, homeopathy, or other non-systemic

307 therapies (i.e., sun exposure), occurred in 937 cases.

308 One hundred-ten of 251 patients (43.8%) temporarily suspended therapy that was restarted

309 during the whole observation period, whereas 141 patients continued to manage AD with topical

310 therapies, emollients, homeopathy or other non-systemic therapies.

311

312 ***Different management of immunosuppressive systemic compounds compared to dupilumab***

313 The majority of patients (86.3%, 1580/1831) continued therapy, whereas 13.7% of patients

314 (251/1831) withdrew systemic therapy at least once, with a mean duration of treatment

315 interruption of 56.5 days (±27.2), and a total number of therapeutic interruptions of 286. Most of

316 treatment interruptions was recorded at timepoint 1 (67.1%, 192/286), whereas in 16.8% (48/286)

317 and 16.2% (46/286) of cases, therapy was withdrawn at timepoint 2 and 3, respectively. Treatment

318 interruptions occurred with similar distribution across the three cohorts of patients treated with

319 systemic immunosuppressive compounds (36.4% of cases with at least one treatment

320 interruption), dupilumab monotherapy (32.9%), or dupilumab combined with other systemic

321 therapies (30.7%). Nevertheless, considering the rate of treatment interruption for each drug,

322 dupilumab was interrupted in only 9.9% (156/1576) of cases, whereas cyclosporine,

323   antihistamines, oral corticosteroids, phototherapy, methotrexate were interrupted in 40.9%

324   (52/127), 39.9% (190/476), 23.4% (34/145), 74.1% (60/81), 23.5% (12/51) of cases, respectively

325   (Table 2).

326   In 39.9% (114/286) of cases, treatment interruption was due to patient decision, while in 5.6%

327   (16/286) and 30.1% (86/286) of cases, treatment interruption was suggested by the general

328   practitioner and by the dermatologist, respectively. In particular, the interruption of systemic

329   immunosuppressive compounds was more frequently suggested by the dermatologist (40.4%,

330   42/104), whereas dupilumab monotherapy or dupilumab combined with other systemic therapies

331   were mostly interrupted because of patient decision (53.2% [50/94]; 50% [44/88] respectively)

332   (Table S2). In details, one or more reasons led to the decision of stopping therapy: (i) the inability

333   to maintain drug supply, other non-medical or unspecified causes (58.7%, 168/286 cases); (ii) the

334   occurrence of concomitant comorbid conditions (5.9%, 17/286 cases); (iii) age, over 60 years old

335   (5.2%, 15/286 cases), (iv) close contact with SARS-CoV-2+ subject (2.4%, 7 /286); (v) SARS-CoV-2

336   infection (2.8%, 8/286); (vi) fear of increased susceptibility to SARS-CoV-2 infection (24.8%,

337   71/286). Fear of increased susceptibility to SARS-CoV-2 infection caused treatment interruption in

338   23.4%, 23.9%, and 26.9% of patients treated with dupilumab monotherapy, dupilumab combined

339   with other systemic therapies, and systemic immunosuppressive compounds, respectively.

340

341   ***Different clinical courses in patients withdrawing treatment compared to patients continuing***

342   ***therapy.***

343   At timepoint 1 (lockdown phase), disease severity assessment of the whole patient population

344   showed: mean EASI score of 6.8 ±7.7, itch-NRS of 2.6 ±2.2, sleep-NRS of 1.7 ±2.1, and self-

345   assessment of AD severity, AD-NRS of 2.5 ±2.1 (Table 3). During the study period, patients

346   experienced a significant reduction of mean itch-NRS, mean sleep-NRS, and mean AD-NRS scores,

achieving lower mean scores at timepoint 3, compared to timepoint 1 (Table S3 and Table S4). This improvement reflected the significant decrease of mean EASI score at timepoint 3 (3.4 ± 4.4) compared to timepoint 1 (6.8 ± 7.7, p<0.0001). Reduction of mean EASI score was observed in both patients continuing treatment and patients interrupting systemic therapy, though at different extent (Table 3). Indeed, mean EASI score changed in the cohort of patients continuing treatment over time (6.6±7.8 at timepoint 1 vs. 2.8±3.4 at timepoint 3), obtaining a 10-fold higher reduction compared to the cohort of patients withdrawing treatment (8.2±7.5 at timepoint 1 vs. 7.3±7.7 at timepoint 3).

Self-assessment of itch, sleep and disease severity did not reveal any marked difference between the two patient subcohorts in terms of score reduction (Table 3).

At timepoint 1, AD improvement was experienced by a higher percentage of patients continuing therapy compared to patients discontinuing treatment (28.8% vs. 15.5%, p<0.001). Stable AD was reported by 60.9% of patients continuing therapy compared to 48.6% of patients interrupting therapy. On the contrary, an increased number of patients discontinuing therapy described worsening of disease compared to patients continuing therapy (35.9% vs. 10.3%). Similarly, AD status perceived by patients continuing or interrupting therapy was significantly different at the following timepoints (p<0.001; Table 3). Comparing patients treated with dupilumab monotherapy, dupilumab combined with other systemic therapies, and immunosuppressive systemic compounds, a reduction of disease severity (EASI score, and NRS scores) was detected at timepoint 3 vs. timepoint 1, as well as a significantly different AD status across the three patient cohorts at each time point (p<0.0001, Table S3). Patients treated with dupilumab monotherapy showed lower disease activity at timepoint 1, with a mean EASI score significantly lower compared to the other patients (p<0.001), and this improvement was sustained thereafter (Table S3).

Discussion

This observational study included a large population of patients (1831 adult subjects) affected by moderate-to-severe AD and treated with systemic therapies or phototherapy, and managed during the COVID-19 pandemic in Italy. The participating centers (n=35) were highly representative of the different incidence distribution of SARS-CoV-2 infection nationwide, having 15, 10, and 10 centers located in Northern, Central, and Southern Italy, respectively.[8] During the observation period, a total number of 240,578 SARS-CoV2 positive cases was registered, with a cumulative number of 190,248 recovered cases and 34,767 deaths.[8] In our study population , less than 1% of patients (16/1831) resulted positive to SARS-CoV-2, with only three patients who required hospitalization, though swab testing was not massively performed throughout the study period. During this critical sanitary emergency, clinical activity in dermatology clinics was markedly limited, and teledermatology (web- and phone- counselling) was extremely useful for reducing patient access to hospital. This modality was well accepted by AD patients who continued to have access to dermatologist consultation, guaranteeing support and treatment continuation in the majority of cases. Indeed, a relatively low number of patients were lost to follow-up (7.7%). As suggested by both national and international scientific societies, most patients were recommended to continue their current treatment during COVID-19 pandemic.[2] About 86% of patients continued treatment, including 8 patients who resulted positive to SARS-CoV-2 infection, albeit common recommendations suggested to withdraw therapy. Notably, 85% of patients included in this study were treated with dupilumab, mostly prescribed as monotherapy.

Considering disease severity assessment, patients undergoing dupilumab monotherapy showed lower disease activity suggesting a better control of AD compared to patients treated with systemic immunosuppressive compounds or dupilumab combined with other systemic therapies. The therapeutic regimen combining dupilumab with other systemic agents occurred in a cohort of

394   patients with significantly higher prevalence of atopic disorders who may require this combined

395   approach as likely they represent a high-need patient population. Response to treatment in these

396   patients resulted similar to patients treated with dupilumab monotherapy or systemic

397   immunosuppressive compounds. This latter class of agents was supposed to have an unfavorable

398   safety profile compared to biologics but no warning signal was detected in our study. Dupilumab,

399   does not impair the immune compartments implicated in host defense against viral infections, and

400   thus may be considered a safer therapeutic choice for AD.[9-12] In general, infection rates in in

401   dupilumab clinical trials resulted similar to placebo, and, in particular, viral infections, such as

402   respiratory infections, were not reported as meaningful adverse event.[7,13]

403   In terms of effectiveness, dupilumab therapy obtained a satisfactory control of the disease and

404   consistently with the other systemic compounds, treatment interruption did not cause a rapid and

405   relevant worsening of the disease, as highlighted by the decrease of both patient-assessed severity

406   scores and EASI score in patients discontinuing therapy. This finding is in line with a recent study

407   reporting maintenance of EASI-75 response in 30.4% of high-responding patients treated with

408   dupilumab, after rerandomization to placebo.[14] However, the reduction of disease severity in

409   patients discontinuing therapy was not associated with a positive patient perception of AD status:

410   a higher percentage of patients withdrawing therapy evaluated their AD status as worsened.

411   Likely, therapy continuation, compared to an intermittent or discontinued therapeutic regimen,

412   might positively impact on patient perception of both disease control and severity.

413   Dupilumab was interrupted in a small percentage of patients, conversely to cyclosporine and oral

414   corticosteroids. In addition, phototherapy was interrupted in most cases (about 74%) due to the

415   lack of accessibility to phototherapy services during phase I (lockdown). Dupilumab interruption

416   was mainly based on patient decision and the main cause of interruption was represented by non-

417   medical reasons (lack of drug supply). Fear of having an increased risk of COVID -19 disease

determined treatment interruption in 25% of patients withdrawing therapy, similarly to recent findings observed in psoriasis patients.[15] Another study confirmed that patients affected by either psoriasis (233 patients) or AD (68 patients) who felt unsafe about their immunomodulatory treatment, were more concerned about having SARS-CoV-2 infection and more likely discontinued therapy during pandemic (overall treatment interruption: 7.3%).[16] In particular, AD patients with asthma were more concerned about being at risk of COVID-19 disease because of AD and its treatment.[16]

The strength of our study is the large AD population treated with systemic therapies who was observed longitudinally, during the national lockdown period (phase I) and the following phase of partial and gradual re-opening of health care services (phase II and III), that were planned in order to face COVID-19 outbreak. However, some limitations related to the management and disease severity evaluation via web- or phone-counselling should be considered as most of the assessment tools used were patient-reported and only a minor percentage of patients could be evaluated by regular visits during phase 3. In addition, most patients were undergoing dupilumab therapy and this could represent a selection bias of the study population likely related to the relatively higher number of dupilumab-treated patients managed in a dedicated AD outpatient clinic.

Data collection on the use of immunomodulants/immunosuppressants during COVID-19 pandemic will continue by the DA-COVID-19 registry, as internationally promoted by the SECURE-AD registry,[17] in order to better delineate the infectious risk related to their use in AD population.

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Figure 1. Timeline with COVID-19 study timepoints and timing of Italian regulation for any kind of activity during COVID-19 pandemic. Phase I (lockdown period), characterized by the complete closing of non-essential health care services by March 10th 2020, followed by phase II starting by May 4th 2020, wherein lockdown restrictions were eased, consisting of a partial and gradual re-opening of elective hospital and ambulatory activities. Phase III of pandemic, starting by June 15th 2020, was characterized by the recovering of health care services, regulated by local sanitary authorities that created a heterogenous management of the outbreak, resulting in a scattered full recovery of healthcare activity across national borders
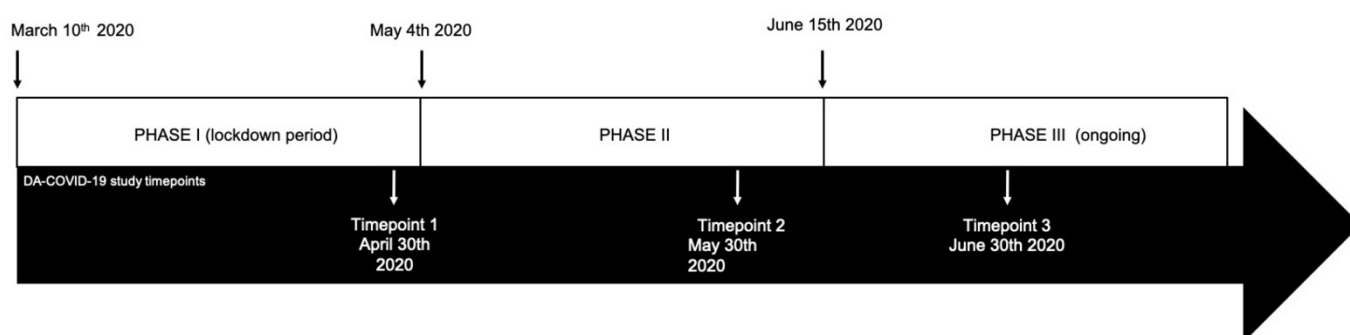
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529 **Table 1.** Clinical and demographic characteristics of patients included in the DA-COVID-19
530 registry, dissecting patients who continued or discontinued therapy as subcohorts.

			Patients continuing treatment	Patients discontinuing treatment	Total
Number of patients (%)			1580 (86.3%)	251 (13.7%)	1831
Age [years] (±SD)			42.3 (17.2)	41.5 (18.2)	42.2 (17.4)
Gender [Males] n pts (%)			867 (54.9%)	132 (52.6%)	999 (54.6%)
Smoking		No	1087 (68.9%)	172 (68.5%)	1259 (68.8%)
		Yes	365 (23.1%)	59 (23.5%)	424 (23.2%)
		Former smoker	126 (8.0%)	20 (8.0%)	146 (8.0%)
Concomitant atopic conditions		Rhinitis	741 (46.9%)	118 (47.0%)	859 (46.9%)
		Conjunctivitis	563 (35.7%)	77 (30.8%)	640 (35.0%)
		Asthma	498 (31.5%)	79 (31.5%)	577 (31.5%)
Timepoint 1 (lockdown- phase 1)	**Stopped Therapy**	By patient decision	-	92 (47.9%)	92
		By dermatologist	-	41 (22.4%)	41
		By general practitioner	-	12 (6.5%)	12
		Unknown	-	47 (24.5%)	47
	Reason for stopping therapy	Any reason		192/286 (67.1%)	
		Fear of SARS-CoV-2 infection	-	62	62
		SARS-CoV-2 infection	-	6	6
		Contact with SARS-CoV-2+ subject	-	7	7
		Comorbidity	-	10	10
		Age > 60 years old	-	6	6
		Other (i.e., drug supply, no mobility, etc)	-	101	101
Timepoint 2 (phase 2)	**Stopped Therapy**	By patient decision	-	14 (28.0%)	14
		By dermatologist	-	22 (43.1%)	22
		By general practitioner	-	3 (6.0%)	3
		Unknown	-	9 (18.7%)	9
	Reason for stopping therapy	Any reason	-	48/286 (16.8%)	48
		Fear of SARS-CoV-2 infection	-	6	6
		SARS-CoV-2 infection	-	2	2
		Contact with SARS-CoV-2+ subject	-	-	-
		Comorbidity	-	5	5
		Age > 60 years old	-	3	3
		Other (i.e., drug supply, no mobility, etc)	-	32	32
Timepoint 3 (phase 3)	**Stopped Therapy**	By patient decision	-	8 (16.7%)	8
		By dermatologist	-	23 (47.9%)	23
		By general practitioner	-	1 (2.1%)	1
		Unknown	-	14 (30.4%)	14
	Reason for stopping therapy	Any reason	-	46 (16.1%)	46
		Fear of SARS-CoV-2 infection	-	3	3
		SARS-CoV-2 infection	-	0	0
		Contact with SARS-CoV-2+ subject	-	0	0
		Comorbidity	-	2	2
		Age > 60 years old	-	6	6
		Other (i.e., drug supply, no mobility)	-	35	35
Missing data about decision of treatment interruption					70 (24.5%)
Number of patients lost to follow up (%)					142 (7.7%)

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534   **Table 2. Therapies prescribed during the study period.**

	Dupilumab	Antihistamines	Systemic corticosteroids	Cyclosporine	Phototherapy	Methotrexate	Azathioprine	Mycophenolate mofetil
N. of total prescriptions	1576	476	145	127	81	51	8	2
N. of prescriptions in monotherapy	1013	38	7	47	30	17	5	0
N. of prescriptions in combination	563	438	138	80	51	34	3	2
Stopped therapy n. (%)	156 (9.9%)	190 (39.9%)	34 (23.4%)	52 (40.9%)	60 (74.1%)	12 (23.5%)	0	0

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Table 3. Disease severity assessed at different timepoints related to therapy continuation or discontinuation. Both patient-assessed severity measurements - itch-NRS score sleep-NRS score AD-NRS score, course of disease (improved, stable, worsened) - and physician-assessed severity measure (EASI score) were performed in all patient population, in the subcohort of patients treated continuously, and in the subcohort of patients who discontinued treatment.

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			Patients continuing treatment (n. pts: 1580)	Patients discontinuing treatment (n. pts: 251)	Total population (n. pts: 1831)
Timepoint 1 (lockdown-phase 1)	Mean EASI score (±SD) ç		6.6 (7.8) #	8.2 (7.5) #	6.8 (7.7)
	Mean itch-NRS score (±SD)		2.4 (2.1)	3.7 (2.3)	2.6 (2.2)
	Mean sleep-NRS score (±SD)		1.6 (2.0)	2.7 (2.4)	1.7 (2.1)
	AD-NRS score (±SD)		2.3 (2.0)	3.5 (2.2)	2.5 (2.1)
	Self-reported AD status §	Improved n. pts (%)	454 (28.8%)	39 (15.5%)	493 (27.0%)
		Stable n. pts (%)	961 (60.9%)	122 (48.6%)	1083 (59.2%)
		Worsened n. pts (%)	162 (10.3%)	90 (35.9%)	252 (13.8%)
Timepoint 2 (phase 2)	Mean itch-NRS score (±SD)		2.4 (2.1)	3.7 (2.3)	2.6 (2.2)
	Mean sleep-NRS score (±SD)		1.5 (1.8)	2.8 (2.8)	1.6 (2.0)
	AD-NRS score (±SD)		2.1 (1.9)	3.7 (2.6)	2.3 (2.1)
	Self-reported AD status §	Improved n. pts (%)	417 (27.2%)	53 (22.1%)	470 (26.5%)
		Stable n. pts (%)	980 (63.8%)	102 (42.5%)	1082 (61.0%)
		Worsened n. pts (%)	138 (9.0%)	85 (35.4%)	223 (12.6%)
Timepoint 3 (phase 3)	Mean EASI score (±SD) ç		2.8 (3.4)	7.3 (7.7)	3.4 (4.4)
	Mean itch-NRS score (±SD)		3.3 (2.6)	3.3 (2.6)	2.2 (2.1)
	Mean sleep-NRS score (±SD)		1.2 (1.7)	2.2 (2.4)	1.3 (1.9)
	AD-NRS score (±SD)		1.9 (1.9)	3.0 (2.4)	2.1 (2.0)
	Self-reported AD status §	Improved n. pts (%)	442 (30.2%)	69 (30.7%)	511 (30.3%)
		Stable n. pts (%)	921 (62.9%)	113 (50.2%)	1034 (61.2%)
		Worsened n. pts (%)	101 (6.9%)	43 (19.1%)	144 (8.5%)
Change in EASI score from timepoint 1 to timepoint 3			-2.8 (7.1)	-0.2 (7.7)	-2.5 (7.2)*
Change in itch-NRS from timepoint 1 to timepoint 3			-0.3 (2.0)	-0.2 (2.7)	-0.3 (2.1)*
Change in sleep-NRS from timepoint 1 to timepoint 3			-0.3 (1.9)	-0.3 (2.8)	-0.3 (2.0)*
Change in AD-NRS from timepoint 1 to timepoint 3			-0.4 (1.8)	-0.3 (2.4)	-0.4 (1.9)*

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Legend: AD, atopic dermatitis; EASI: Eczema Area and Severity Index; NRS: Numeric Rating Scale; pts: patients; SD: standard deviation. # $p<0.001$, Wilcoxon rank-sum test was used to compare the 2 patient subcohorts at timepoint 1; § $p<0.001$, Chi square test was used for statistical analysis; ç mean EASI score was calculated on 1831 and 746 patients at timepoint 1 and 3, respectively; * $p<0.0001$, paired T test was used to compare T1 vs. T3 in the total population.

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