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Incidence and severity of COVID-19 in patients with autoimmune blistering skin diseases: A nationwide study

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3 **Incidence and Severity of COVID-19 in patients with autoimmune blistering skin diseases:**
4 **a nation-wide study**

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56

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67

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85 Dear editor,

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87 Since the beginning of the pandemic, the incidence and severity of coronavirus disease-2019
88 (COVID-19) among patients with autoimmune bullous skin diseases (AIBD) has not been
89 characterized in large populations(1-3). We assessed the severity and mortality of COVID-19 in
90 patients with AIBD, with a special interest in a potential risk factor related to previous treatment
91 with rituximab.

92 This study was performed from February to June 2020. in 49 Dermatology Departments located
93 in 12 administrative regions of France. Possible (suggestive clinical symptoms and contact with
94 COVID-19), probable (suggestive CT scan), and confirmed (by reverse transcriptase-
95 polymerase-chain-reaction) cases of COVID-19 with AIBD were identified with data from the
96 hospitals' electronic-health-records for hospitalized patients, and by spontaneous reporting for
97 non-hospitalized patients. Patients who had received at least one infusion of rituximab from
98 September 2019 to June 2020 were identified from the database of each hospital pharmacy.
99 Hospitalization of patients with AIBD and COVID-19, and COVID-19-related death were
100 recorded. Region- and age-specific incidence and lethality of hospitalized confirmed COVID-19
101 in the general population were retrieved from the Santé Publique France website. Detailed
102 methodology is available in supplemental data.

103

104 Of 5180 patients with AIBD, 59 were diagnosed with possible, probable or confirmed COVID-
105 19 of whom 30 (50.8%) were hospitalized, 7 (11.9%) were admitted to an Intensive Care Unit,
106 and 15 (25.4%) died. We identified 21 bullous pemphigoid, 19 mucous membrane pemphigoid,
107 18 pemphigus and 1 pregnant pemphigoid (Table1).

108 The age- and region-standardized incidence ratio of hospitalized confirmed COVID-19 infection
109 was 0.42 (95% CI: 0.20-0.80, p=0.005) for bullous pemphigoid, 1.02 (95% CI: 0.37-2.26;
110 p=0.91) for pemphigus, and 1.18 (95% CI: 0.55-2.23; p=0.62) for mucous membrane
111 pemphigoid. The apparently low risk of COVID-19 infection in patients with Bullous
112 Pemphigoid must therefore be interpreted with caution since it is very likely that some elderly
113 BP patients in poor general condition died from an undiagnosed COVID-19 infection in their
114 nursing home, The incidence ratio (IR) of COVID-19 in patients treated with rituximab ranged
115 from 3.62 (95% CI=1.29-8.85) in AIBD patients hospitalized with a confirmed diagnosis of
116 COVID-19, to 5.37 (95%CI=3.15-8.96) in patients with a confirmed, probable or possible
117 diagnosis of COVID-19 infection (Table 2) .

118 Lethality of hospitalized confirmed COVID-19 (n=8/21, 38.1%) was 1.63-fold (95%CI=0.83-
119 2.55; p=0.13) higher in patients with AIBD than in the general population of the same age
120 (23%). Patients with AIBD and COVID-19 had a 5.9 (95%CI=3.9-8.4) higher 3-month death
121 risk than patients with AIBD without COVID-19 (4-5). Patients with AIBD and a hospitalized or
122 lethal form of COVID-19 were older than those with a benign form (77.9±11.2 versus 65.0±19.3
123 years; p=0.006).

124 The major finding of this study is the notably higher risk of COVID-19 infection in AIBD
125 patients treated with rituximab, corresponding to a more than 5-fold higher incidence of COVID
126 infection than in patients who did not receive rituximab. Patients with AIBD and COVID-19 had
127 a 5.9-fold higher risk of dying during the first wave of the COVID-19 pandemic in France than
128 patients with AIBD and without COVID-19.

129 Overall, this study showed that treatment with rituximab is a major risk factor of COVID-19
130 infection. . Given the high lethality of COVID-19 in patients with AIBD, physicians should
131 carefully evaluate the benefit-risk balance of rituximab therapy during this pandemic period.

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150 Table 1: Age, gender, main comorbidities, AIBD treatments and management (hospitalization versus
 151 outpatient management) of COVID-19 infected patients depending on the type of AIBD

	BP n (%)	MMP n (%)	Pemphigus n (%)	PG n (%)
COVID-19				
confirmed	9 (42.9)	13 (68.4)	6 (33.3)	1 (100)
probable	4 (19)	3 (15.8)	1 (5.6)	0 (0)
possible	8 (38.1)	3 (15.8)	11 (61.1)	0 (0)
Sex, M/F	10/11	6/13	9/9	0/1
Age, years, mean ± SD	81.8 ± 8.2	74.9 ± 12.2	60.9 ± 18.1	32
Body mass index, kg/m ² , mean ± SD	26.2 ± 7.3	27.5 ± 5.4	26.0 ± 4.5	NA
Karnofsky score, mean ± SD	54.5 ± 21.1	67.4 ± 21.0	76.5 ± 39.0	90
Medical history				
diabetes mellitus	11 (52.4)	6 (31.6)	2 (11.1)	0 (0)
hypertension	11 (52.4)	2 (10.5)	3 (16.7)	0 (0)
renal disorder	5 (23.8)	1 (5.3)	0 (0)	0 (0)
cardiovascular disorder	5 (23.8)	3 (15.8)	0 (0)	0 (0)
lung disorder	5 (23.8)	3 (15.8)	1 (5.6)	0 (0)
neurological disorder	5 (23.8)	2 (10.5)	2 (11.1)	0 (0)
neoplasia	7 (33.3)	2 (10.5)	1 (5.6)	0 (0)
dyslipidemia	3 (14.3)	0 (0)	1 (5.6)	0 (0)
other	3 (14.3)	3 (15.8)	0 (0)	0 (0)
Treatment of AIBD* (non-exclusive)				
Systemic corticosteroids	5 (23.8)	3 (15.8)	4 (22.2)	1 (100)
Topical corticosteroids	12 (57.1)	6 (31.6)	2 (11.1)	0 (0)

Conventional immunosuppressants	7 (33.3)	3 (15.8)	1 (5.6)	0 (0)
Rituximab	1 (4.8)	9 (47.4)	13 (72.2)	0 (0)
Dapsone	1 (4.8)	14 (73.7)	0 (0)	0 (0)
Omalizumab	1 (4.8)	2 (10.5)	0 (0)	0 (0)
Cyclines	1 (4.8)	4 (21.1)	0 (0)	0 (0)
Sulfasalazine	0 (0)	2 (10.5)	0 (0)	0 (0)
Management of COVID-19 (non-exclusive)				
Hospitalization	12 (57.1)	10 (52.6)	1 (5.6)	0 (0)
Intensive care unit	1 (4.8)	1 (5.3)	5 (27.8)	0 (0)
Outpatient management	8 (38.1)	8 (42.1)	12 (66.7)	1 (100)

152 *During the previous 9 months

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156 Table2 : Proportions of patients with a confirmed, probable or possible diagnosis of COVID-19
 157 infection among patients with AIBD, according to whether or not they were treated with
 158 rituximab.

159

	AIBD patients treated with rituximab	AIBD patients who did not receive rituximab	Incidence ratio [95% CI]
Diagnosis of COVID-19	n/N (%)	n/N (%)	
Possible, probable or confirmed	22/516 (4.26%)	37/4664 (0.79%)	5.37 [3.15 - 8.96]
Probable or confirmed	13/516 (2.52%)	24/4664 (0.51%)	4.90 [2.43 - 9.40]
Confirmed and hospitalized	6/516 (1.16%)	15/4664 (0.32%)	3.62 [1.29 - 8.85]

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165 **Supplemental data**

166 **Methods**

167 Between February 1st and June 30th, 2020, 49 Dermatology Departments in France (29 university
168 hospitals and 20 general hospitals) identified cases of COVID-19 diagnoses among patients with AIBD
169 followed in their centers. Patients with COVID-19 hospitalized in COVID units or Intensive Care Units
170 (ICU) of the hospital with a corresponding Dermatology Department were systematically identified with
171 structured data of Electronic Health Records (EHR). Other patients with COVID-19, including those who
172 were not hospitalized, treated in ambulatory settings or in nursing homes, and those who were
173 hospitalized in other hospitals were spontaneously reported by dermatologists if they had knowledge of
174 them. Thus, some patients with COVID-19 may not have been tracked.

175

176 These 49 Dermatology Departments were located in 12 administrative regions of France (Ile de France,
177 Grand Est, Bourgogne-Franche Comté, Hauts de France, Provence-Alpes-Côte d'Azur, Auvergne-Rhône
178 Alpes, Centre-Val de Loire, Pays de la Loire, Normandie, Bretagne, Occitanie and Nouvelle Aquitaine).
179 This administrative area corresponded to a combined population size of 64.9 million inhabitants in
180 January, 2020 according to the French National Institute of Statistics and Economic Studies (INSEE)
181 (<https://www.insee.fr/fr/statistiques/4277615?sommaire=4318291>).

182 .

183 COVID-19 cases among patients with AIBD were classified as i) confirmed when COVID-19 reverse
184 transcriptase-polymerase chain reaction (RT-PCR) was positive, ii) probable when RT-PCR was negative
185 or not done, but clinical symptoms were suggestive and chest CT scan showed images suggestive of
186 COVID-19 infection, and iii) possible in patients who had suggestive clinical symptoms and contact with
187 a COVID-19 infected case. Despite the uncertainty of the COVID-19 diagnosis, we considered these
188 latter cases, as they were quite frequent in particular among patients with BP living in nursing homes.

189 For each case (confirmed, probable or possible), the patient's age, sex, comorbidities, clinical symptoms,
190 outcome (recovery or death) and AIBD treatments during the nine-month period prior to the COVID-19
191 diagnosis were recorded. In addition, all Dermatology Departments provided the total number of patients
192 with AIBD they followed, who were identified using the EHR of each center.

193 To specifically examine the risk of COVID-19 infection in patients treated with rituximab, we identified
194 all patients who had received at least one infusion of rituximab from 1st of September 2019 to 1st of June
195 2020 from the database of each hospital pharmacy. This allowed us to identify all patients treated with
196 rituximab among the whole population of patients with AIBD, since rituximab infusions are
197 systematically performed during a hospital stay in France. We could not record the number of patients
198 who had received conventional immunosuppressants among the whole population of patients with AIBD
199 in a similar manner, since these drugs are provided by each patient's usual pharmacist.

200 The number of COVID-19 cases and the age and sex distribution in the general population were obtained
201 from the Santé Publique France website: [https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-](https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-relatives-a-lepidemie-de-covid-19)
202 [relatives-a-lepidemie-de-covid-19](https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-relatives-a-lepidemie-de-covid-19). This registry includes the cumulative number of patients who were
203 hospitalized with RT-PCR-confirmed COVID-19, the cumulative number of deaths by geographical area,
204 sex and 10-year age groups.

205 The age and sex distribution of the general population in France was obtained from the INSEE
206 (<https://www.insee.fr/fr/statistiques/1913143?sommaire=1912926>). The risk of death by year of age in the
207 general population was obtained from the Institut National des Etudes Démographiques (INED) website
208 (https://www.ined.fr/fichier/s_rubrique/193/copie.de.fm_t68.3.fr.xls).

209 The relative distribution of specific AIBD at diagnosis was obtained from the French REGIBUL registry:
210 proportion of pemphigus, BP, mucous membrane pemphigoid (MMP) at diagnosis. The age and sex
211 distribution at diagnosis was obtained from the same registry. Mortality rates were obtained from large
212 epidemiological studies conducted in France. COVID-19 was defined as severe in case of hospitalization
213 for oxygen therapy, hospitalization in an ICU, or death.

214 The statistical analysis plan, including the estimation of distributions of types of AIBD and age
215 distributions of patients with AIBD, the estimation of the expected incidence of hospitalized COVID-19
216 by type of AIBD, the estimation of the standardized-incidence-rates (SIR) for patients with AIBD, the
217 intra-hospital lethality of confirmed COVID-19, and the relative risk of mortality of patients with AIBD
218 and COVID-19 compared to patients with AIBD without COVID-19, is provided in the Supplementary
219 Appendix.

220 This study was approved by the institutional review board of Rouen University Hospital. (No E2020-59)
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