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SHORT PAPER

COVID-19 knowledge prevents biologics discontinuation: Data from an Italian multicenter survey during RED-ZONE declaration

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Abstract

SARS-CoV-2 become pandemics and there is still a dearth of data about its the potentially among dermatological patients under biologics. We aimed to assess health literacy, disease knowledge, treatment dissatisfaction and biologics attitudes toward COVID-19. We performed a cross-sectional, questionnaire-based survey on 98/105 consecutive dermatological patients treated with biologics—51 suffering from plaque psoriasis, 22 from atopic dermatitis, and 25 from hidradenitis suppurativa. An ad hoc, validated questionnaire has 44 items investigating the following domains: knowledge of COVID-19 related to (a) epidemiology, (b) pathogenesis, (c) clinical symptoms, (d) preventive measures, and (e) attitudes. Patients data and questionnaires were collected. Despite only 8.1% thought that biologics may increase the risk of COVID-19, 18.4% and 21.4% of the patients were evaluating the possibility to discontinue or modify the dosage of the current biologic therapy, respectively. Globally, male patients (P = .001) with higher scholarity level (P = .005) displayed higher knowledge of COVID-19. Patients with lower DLQI (P = .006), longer disease duration (P = .051) and lower scholarity (P = .007) have thought to discontinue/modify autonomously their biologic therapy. At the multivariate logistic regression, only the knowledge of epidemiology and preventive measures resulted independent predictors of continuation vs discontinuation and modification vs no modification, respectively. Dermatologists should promote COVID-19 knowledge to prevent biologics disruption.

KEYWORDS

atopic dermatitis, biologics, COVID-19, COVID-19 questionnaire, hidradenitis suppurativa, psoriasis, SARS-CoV-2

1 | INTRODUCTION

Since late December 2019 from Wuhan (Hubei province, People's Republic of China) a new Coronavirus, also known as SARS-CoV2, has spread out in neighboring countries leading the Director-General of the World Health Organization (WHO) to declare pandemics on March 11, 2020.[1,2] Rapidly, Italy has become red-zone with the highest rate of COVID-19 confirmed, hospitalized and deceased patients in Europe; thus to handle this massive health emergency several medical departments were reconverted in COVID-19-dedicated or partially dedicated units, dermatology had promoted telemedicine and maintained face-to-face visits only for urgent patients (ie, melanoma surgery) and chronic patients under certain systemic drugs (ie, biologics and other immunosuppressants).[3]

Paolo Pigatto and Giovanni Damiani contributed equally to this work.

COVID-19 pandemic has forced everyone to use personal protective equipment (PPE), such as goggles, N95 masks, double-layers gloves, and face-shields, and to follow methodically sanitization protocols.[2] Hence, health care workers due to too scrupulous and continuous hand-washing and use of preventive measures and protective equipment could develop hand eczema and related skin disorders.[4] Lan and colleagues recruited a sample of 542 health care and in 97% of them they found a dermatological disorder related to the personal protective equipment (PPE) and to the preventive measures, mainly affecting the nasal bridge, the hands, the cheeks and the forehead, with dryness and desquamation being the most commonly reported symptoms/signs.[5]However, mainly occupational aspects have been investigated so far.

To the best of our knowledge, there is a dearth of data concerning the COVID-19 perceptions of dermatological patients under biologics, a therapy traditionally associated to an increased risk of infections.[6-9] This aspect is of particular interest since it may affect the patients' compliance leading to treatment discontinuation or autonomous modifications.[10] Although biologics have revolutionized the management of chronic dermatological disorders, their interplay between disease, disease activity, and its pharmacological treatment is complex and multifaceted, and sometimes drug-related side effects may occur (ie, airway infections). Side effects are also capable to detriment dermatologist-patients relationship leading to a decreased compliance.[11] Furthermore, also inside the dermatological field the attitude towards biologics are discordant[12,13] due to the dearth of available data.

In these historical and scientific context of uncertainty, in which hospitals are overwhelmed by COVID-19 emergency and at the same time are struggled also by the normal routine (acute patients and chronic ones), we decided to perform a study to assess how COVID-19 impacts patients under biologics to optimize our daily approach.

2 | MATERIAL AND METHODS

2.1 | Ethical clearance

The protocol study of the present investigation was in-depth reviewed, respected the ethical principles of seventh Helsinki Declaration and received full ethical clearance by the involved Institutions. All patients signed a written consent form.

2.2 | Patients selection: inclusion and exclusion criteria

This cross-sectional, questionnaire-based survey was performed in February 10, 2020, before the declaration of pandemics, in three primary referral dermatological centers, IRCCS Galeazzi Orthopedic Istitute, IRCCS San Donato, both in Milan, and IRCCS San Gallicano in Rome. All the clinical evaluations were coherent with Italian Society of Dermatology, Venereology and Sexual Transmitted Diseases (SIDEMAST) recommendations during COVID-19 pandemics (www.sidemast.org/blog/coronavirus). Patients scheduled for these days were consecutively enrolled if they met the eligible criteria.

Patients were enrolled in the present study if meeting the following inclusion criteria: (a) aged ≥18 years, (b) diagnosis of plaque psoriasis, atopic dermatitis or hidradenitis suppurativa performed by two independent board-certified dermatologists lasting more than 5 years ago, (c) with a severity.

- in psoriatic patients: Psoriasis Area Severity Index (PASI)[14] ≥10 and or Disease Activity index for PSoriatic Arthritis" (DAPSA)[15] > 14 before starting the systemic treatment and a stable disease (Delta PASI or Delta DAPSA in two consecutive controls <10%) at the study baseline;
- in atopic dermatitis patients with Eczema Area and Severity Index (EASI)[16] >22 before starting the systemic treatment and a stable disease (Delta EASI in two consecutive controls <10%) at the study baseline;
- in HS patients with Hurley III[17] and International Hidradenitis Suppurativa Severity Score System (IHS4)[18] >10 before starting the systemic treatment and a stable disease (Delta IHS4 in two consecutive controls <10%) at the study baseline,

(d) under biologics treatment for >1 year.

Patients were excluded if: (a) history or actual diagnosis of psychiatric disease, (b) diagnosed degenerative neurological disease (acquired or congenital), (c) previous chemotherapy, (d) brain tumor, (e) drug addictions, (f) <1 year of treatment with biologics, (g) <5 years disease duration.

Remarkably, in these departments patients undergoing a biological therapy were affecting only by psoriasis (PsO), or atopic dermatitis (AD) or hidradenitis suppurativa (HS).

2.3 | Dermatological assessment

After verifying medical history and demographics already recorded in the database, two board-certified, independent dermatologists clinically assessed the enrolled patients collecting the appropriate severity scores in compliance with the Italian guidelines.[19-23]

AD patients were evaluated using Dermatologic Quality of Life Score (DLQI)[23,24] and Eczema Area and Severity Index (EASI). PsO patients were evaluated using DLQI, PASI and DAPSA (if psoriatic arthritis was co-diagnosed), whilst HS patients underwent DLQI, Hurley score, IHS4 and Autoinflammatory Disease Damage Index (ADDI).[25]

2.4 | Questionnaire development

A validated questionnaire consisting of 44 items was administered to a cohort of patients with dermatological disorders[26] (Supplementary material 1). The questionnaire was comprised of five sections: the first assessed the risk perception about the likelihood of becoming

infected by the SARS-CoV2 and negative attitudes towards the pharmacological treatment, the second explored the knowledge regarding the virus, the third the knowledge concerning the clinical symptoms and manifestations, the fourth preventive measures that can be implemented against COVID-19 and, finally, the fifth the risk perception.

2.5 | Statistical analysis

Before commencing any statistical analyses, data were visually inspected for capturing potential outliers. Descriptive statistics was performed, by expressing values as means ± SDs. Scores were also assessed in terms of kurtosis and skewness. Regression analyses were carried out to shed light on the determinants of the knowledge score. All statistical analyses were carried out by means of the commercial software "Statistical Package for Social Sciences" (SPSS version 24 for Windows, IBM Corporation, Armonk, New York). Graphs were generated by means of the commercial software MedCalc Statistical Software (version 18.11.3, MedCalc Software bvba, Ostend, Belgium, 2019). All figures with *P*-values less than or equal to .05 were considered statistically significant.

3 | RESULTS

3.1 | Clinical and demographic data

We interviewed 105 consecutive dermatological patients under biologics and 98 (93.3%) were enrolled, 51 (52.0%) suffering from plaque psoriasis, 22 (22.4%) from atopic dermatitis, and 25 (25.5%) from hidradenitis suppurativa. Among psoriatic patients only 27/51 (52.9%) have also psoriatic arthritis. The mean age in the enrolled patients was 44.36 ± 8.45 years (median 43 years) (PsO: 46.35 ± 9.02, AD: 40 ± 6.90, HS: 44.12 ± 7.18) with a mean disease duration of 17.77 ± 7.19 years (median 17 years) (PsO: 17.35 ± 7.07, AD: 21.55 ± 8.07, HS: 15.28 ± 5.28). Median DLQI was 12 (12.3 ± 2.8) (PsO: 10.86 ± 2.47, AD: 13.68 ± 2.38, HS: 14.16 ± 2.17). PASI and DAPSA among psoriatic patients were 2.9 ± 2.2 (median 3) and 6.2 ± 3.7 (median 6). In HS patients IHS4 and ADDI were 7.8 ± 3.4 (median 8) and 2.7 ± 0.8 (median 3) respectively. In AD patients the EASI was 7.8 ± 2.6 (median 8). From a therapeutic point of view, the enrolled patients underwent Adalimumab (n = 36, 36.7%), Dupilumab (n = 22, 22.4%), Etanercept (n = 13, 13.3%), Ustekinumab (n = 10, 10.2%), Ixekizumab (n = 8, 8.2%), Secukinumab (n = 7, 7.1%) and Certolizumab 2 (2.0%). Further details are shown in Table 1.

TABLE 1 Main characteristics of the recruited sample

Variable	Value
Sociodemographic parameters	
Age	44.36 ± 8.45 (43)
Gender	
Male	51 (52.0%)
Female	47 (48.0%)
Family history	38 (38.8%)
Scholarity	
Primary school	3 (3.1%)
Middle school	14 (14.3%)
High school	35 (35.7%)
University	35 (35.7%)
PhD/master	11 (11.2%)
Disease	
Plaque psoriasis	51 (52.0%)
Hidradenitis suppurativa	25 (25.5%)
Atopic dermatitis	22 (22.4%)
Disease severity	
Disease duration	17.77 ± 7.19 (17)
DLQI	12.3 ± 2.8 (12)
Psoriasis	
PASI	2.9 ± 2.2 (3)
DAPSA	6.2 ± 3.7 (6)
Hidradenitis suppurativa	
IHS4	7.8 ± 3.4 (8)
ADDI	2.7 ± 0.8 (3)
Atopic dermatitis	
EASI	7.8 ± 2.6 (8)
Biologic therapies	
Adalimumab	36 (36.7%)
Dupilumab	22 (22.4%)
Etanercept	13 (13.3%)
Ustekinumab	10 (10.2%)
Ixekizumab	8 (8.2%)
Secukinumab	7 (7.1%)
Certolizumab	2 (2.0%)

Abbreviations: ADDI, Autoinflammatory Disease Damage Index; DAPSA, Disease Activity Index for PSoriatic Arthritis; DLQI, Dermatologic Life Quality Score; EASI, Eczema Area and Severity Index; IHS4, International Hidradenitis Suppurativa Severity Score System; PASI, Psoriasis Area Severity Index.

3.2 | COVID-19 risk perceptions and relative attitudes

Scores for each domain and for the overall questionnaire are reported in Table 2. Noteworthy, no differences among the disease groups could be found, so the entire sample of dermatological patients was analyzed in an aggregated manner (Figure 1). SARS-CoV2 infection worried half of the interviewed patients, in particular 25 (25.6%) were really worried, 24 (24.5%) moderately worried, 29(29.6%) a little worried and 20 (20.4%) not worried at all.

Remarkably, 28 (28.6%) patients perceived that their chronic dermatological disease expose them to a moderate-to-severe risk to contract SARS-CoV2, whereas 17.3% and 54.1% regard it as low or null. Despite only 8.1% thought that biologics expose them to a moderate to severe risk to contract SARS-CoV2, 18.4% and 21.4% of the whole patients declared that they have assessed the possibility to discontinue or modify the dosage of the current biologic therapy, respectively.

TABLE 2 Scores of each domain of the questionnaire utilized in the present study

	Value		Range	
Questionnaire domain	Mean	SD	Minimum	Maximum
COVID-19 related epidemiology	39.22	5.00	27	57
COVID-19 related pathogenesis	28.64	5.57	0	42
COVID-19 related clincal symptoms	25.40	5.43	13	37
COVID-19 related prevention	12.12	2.79	6	18
COVID-19 related attitudes	12.39	2.29	9	18
Total COVID-19 related knowledge and attitudes score	117.78	9.41	71	136

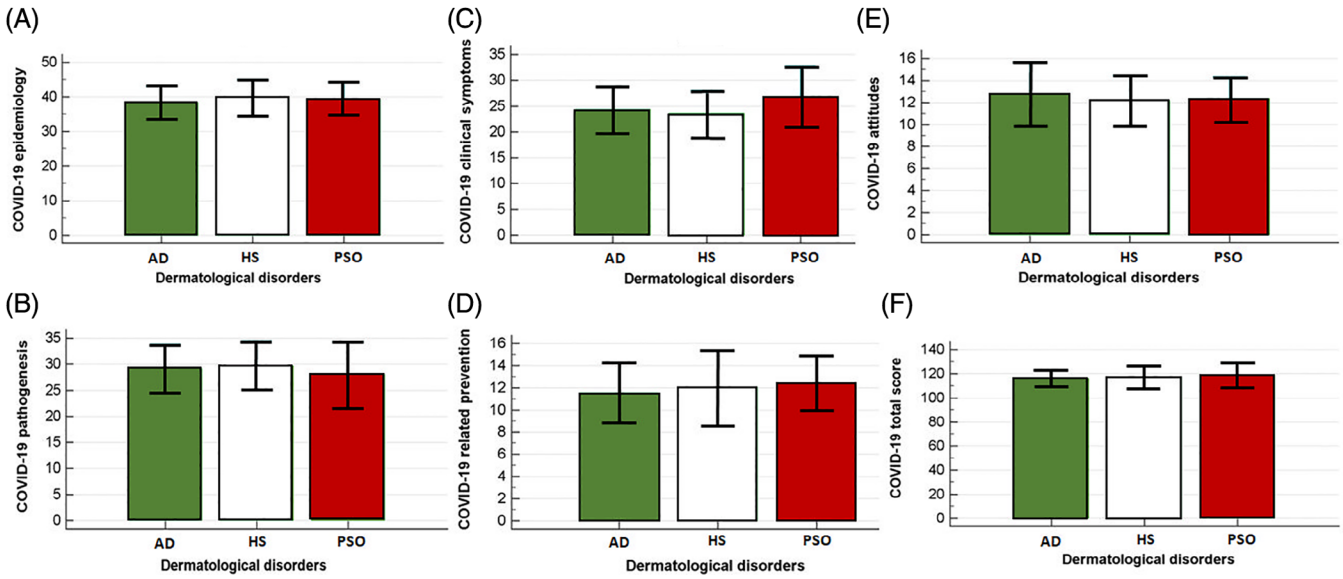

FIGURE 1 Knowledge score of COVID-19 related risk perceptions and epidemiology, A; pathogenesis, B; clinical symptoms, C; preventive measures, D; attitudes, E; and overall score, F; stratified according to the dermatological disorders of the patients recruited (atopic dermatitis. Hidradenitis suppurativa and plaque psoriasis)

3.3 | Clinical variables influencing COVID-19 questionnaire domains

At the multivariate regression analysis, knowledge regarding the virus epidemiology was found to correlate with male gender (coefficient regression 2.59, P = .01) and scholarity level (coefficient regression 1.80, P = .0003).

Knowledge of COVID-19 related pathogenesis was associated with DLQI (coefficient regression 0.61, P = .0061) and inversely with scholarity level (coefficient regression −1.03, P = .0620, significantly borderline).

Knowledge concerning clinical symptoms inversely correlated with DLQI (coefficient regression −0.80, P = .0001), and directly with scholarity level (coefficient regression 1.40, P = .0058).

Knowledge concerning prevention inversely correlated with DLQI (coefficient regression −0.33, P = 0.0019) and positively with scholarity level (coefficient regression 1.00, P = .0002).

COVID-19 related attitudes (drug continuation vs modification/discontinuation) directly correlated with DLQI (coefficient regression 0.24, P = .0059), disease duration (coefficient regression 0.07, P = .0513, statistically borderline) and inversely with scholarity (coefficient regression −0.59, P = .0077).

Globally male patients (coefficient regression 6.97, P = .0003) with higher scholarity level (coefficient regression 2.57, P = .0049) displayed higher knowledge of COVID-19. Further details are reported in Table 3.

3.4 | Therapy attitudes and COVID-19 questionnaire

Stratifying according to continuation vs discontinuation and no modification vs modification in drug dose/schedule, statistically significant differences in terms of knowledge of COVID-19 related epidemiology, pathogenesis, clinical symptoms and preventive measures (all, P-value <.001) were found. Noteworthy, scores were higher in the continuation/no modification group, except for knowledge of COVID-19 related pathogenesis, for which higher scores were reported in the discontinuation/modification group. No differences could be found in terms of age, gender distribution, scholarity level, family history,

TABLE 3 Multivariate regression analyses for the scores of each domain and the overall score of the COVID-19 related knowledge and attitudes questionnaire utilized in the present study

Independent variables	Coefficient	SE	*t*	*P*	$r_{partial}$	$r_{semipartial}$
COVID-19 related knowledge concerning epidemiology						
(Constant)	36.78					
Age	0.04	0.07	0.52	.6069	.05	.05
Male gender	2.59	0.98	2.63	.0100	.27	.25
Disease	−0.70	0.75	−0.93	.3531	−.10	.09
Disease duration	−0.12	0.08	−1.55	.1238	−.16	.15
Family history	−0.59	0.98	−0.60	.5523	−.06	.06
DLQI	−0.21	0.19	−1.10	.2740	−.12	.10
Scholarity	1.80	0.48	3.78	.0003	.37	.35
COVID-19 related pathogenesis						
(Constant)	24.61					
Age	−0.02	0.08	−0.27	.7919	−.03	.03
Male gender	1.81	1.13	1.60	.1129	.17	.15
Disease	0.17	0.86	0.20	.8458	.02	.02
Disease duration	−0.03	0.09	−0.30	.7617	−.03	.03
Family history	0.27	1.13	0.24	.8145	.02	.02
DLQI	0.61	0.22	2.81	.0061	.28	.27
Scholarity	−1.03	0.55	−1.89	.0620	−.20	.18
COVID-19 related knowledge concerning clinical symptoms						
(Constant)	30.82					
Age	−0.01	0.07	−0.11	.9155	−.01	.01
Male gender	1.69	1.03	1.65	.1022	.17	.15
Disease	−0.12	0.78	−0.15	.8786	−.02	.01
Disease duration	−0.02	0.08	−0.25	.8061	−.03	.02
Family history	−0.46	1.03	−0.45	.6518	−.05	.04
DLQI	−0.80	0.20	−4.06	.0001	−.39	.36
Scholarity	1.40	0.50	2.83	.0058	.29	.25
COVID-19 related knowledge of preventive measures						
(Constant)	13.58					
Age	0.003	0.04	0.10	.9230	.01	.01
Male gender	0.72	0.53	1.34	.1835	.14	.12
Disease	−0.32	0.41	−0.80	.4289	−.08	.07
Disease duration	−0.02	0.04	−0.55	.5850	−.06	.05
Family history	−0.42	0.53	−0.79	.4317	−.08	.07
DLQI	−0.33	0.10	−3.19	.0019	−.32	.29
Scholarity	1.00	0.26	3.87	.0002	.38	.35
COVID-19 related attitudes						
(Constant)	8.7714					
Age	0.01	0.03	0.22	.8288	.02	.02
Male gender	0.16	0.45	0.36	.7217	.04	.03
Disease	0.35	0.34	1.02	.3090	.10	.10
Disease duration	0.072	0.04	1.98	.0513	.20	.18
Family history	0.33	0.45	0.72	.4718	.08	.07
DLQI	0.24	0.09	2.82	.0059	.29	.26
Scholarity	−0.59	0.22	−2.73	.0077	−.28	.25

(Continues)

TABLE 3 (Continued)

Independent variables	Coefficient	SE	*t*	*P*	$r_{partial}$	$r_{semipartial}$
COVID-19 related total knowledge and attitudes score						
(Constant)	114.56					
Age	0.02	0.13	0.14	.8930	.01	.01
Male gender	6.97	1.84	3.79	.0003	.37	.35
Disease	−0.62	1.40	−0.44	.6578	−.05	.04
Disease duration	−0.12	0.15	−0.83	.4085	−.09	.08
Family history	−0.88	1.84	−0.48	.6335	−.05	.04
DLQI	−0.48	0.35	−1.35	.1791	−.14	.13
Scholarity	2.57	0.89	2.89	.0049	.29	.27

Abbreviation: DLQI, Dermatologic Life Quality Index; SE, standard error.

TABLE 4 Univariate analysis showing statistically significant differences between continuation/no modification and discontinuation/modification groups

Domain	Continuation	Discontinuation	*P*-value	No modification	Modification	*P*-value
Epidemiology	40.45 ± 4.31	33.78 ± 4.07	< .001	40.60 ± 4.24	34.19 ± 4.24	< .001
Pathogenesis	27.86 ± 4.33	32.11 ± 8.64	< .001	27.57 ± 4.24	32.57 ± 7.85	< .001
Clinical symptoms	26.70 ± 4.94	19.61 ± 3.46	< .001	26.97 ± 4.64	19.62 ± 4.08	< .001
Preventive measures	12.74 ± 2.66	9.39 ± 1.29	< .001	12.97 ± 2.45	9.00 ± 1.34	< .001

disease type, disease duration and DLQI score. More details are shown in Table 4.

At the multivariate logistic regression, only knowledge of COVID-19 -related epidemiology (OR 0.81 [95%CI 0.67-0.98], *P* = .0334) and of COVID-19-related preventive measures (OR 0.54 [95%CI 0.34-0.5], *P* = .0075) resulted independent predictors (more precisely, protective factors) of continuation vs discontinuation and modification vs no modification, respectively (Table 5).

4 | DISCUSSION

During COVID-19 pandemics ∼40% of dermatological patients under biologics have thought to autonomously modify or even discontinue their therapy.

SARS-CoV2 displayed a special tropism for respiratory epithelium, thus it may cause respiratory symptoms of different severity spacing from mild cough to death in 7.2% of the cases in Italy.[27,28] Since COVID-19 pathogenesis involved mainly respiratory airways, patients with respiratory comorbidities might have higher risk, but at the moment no data are present to confirm it.[29] In literature, both psoriasis, atopic dermatitis and hidradenitis suppurativa displayed an higher risk of respiratory comorbidities; in accord with this evidence ∼30% of the interviewed patients thought that their dermatological disease could increase the SARS-CoV2 infection risk.

Psoriatic patients displayed a baseline airway inflammation,[30,31] that may lead to the epidemiologically proven increased risk of asthma, and chronic obstructive pulmonary disease (COPD).[32] AD theory of "atopic march" gives the pathogenetic rationale to the increased asthma risk found in atopic patients.[33] Then, HS and PsO patients, there is an high prevalence of smokers and in both disease smoking increase the severity and flares.[34,35] Interestingly, Lippi and colleagues found that active smoking is not correlated with COVID-19 severity.[36]

Beside the direct effects of the dermatological disease, the impact of biologics on SARS-CoV2 infection risk were regarded as negligible in our patients, in fact only 1 in 10 interviewed patients thought that biologics may increase their risk to contract COVID-19. Despite only 8.1% thought that biologics expose them to a moderate to severe risk to contract COVID-19, 18.4% and 21.4% of the whole patients declared that they have assessed the possibility to discontinue or modify the dosage of the current biologic therapy, respectively.

Biologics have revolutionized the treatment and management of chronic dermatological disorders, but they also have increased the rate of airway infections, especially for psoriasis and hidradenitis suppurativa.[12,13,36,37] Conversely, in a recent meta-analysis Zayed and colleagues did not find an increased risk of airway infections in AD patients with asthma undergoing dupilumab.[38] No data are still present about the SARS-CoV2 increased risk of infection in patients undergoing biologics, but the present literature may justify the therapeutic doubts occurred in ∼40% of our patients. Otherwise, transplanted patients undergoing immunosuppressants, communed by a dysfunctional immune system seem to not have an increased risk to contract Coronavirus.[39,40]

Our data suggest that the knowledge about COVID-19 may influence the therapy discontinuation, in fact COVID-19-related

TABLE 5 Multivariate logistic regression analyses shedding light on the determinants of continuation vs discontinuation and modification vs no modification of biologic therapies in the considered sample of dermatological patients

Variable	Coefficient	SE	Wald	*P*-value	OR	95%CI
Continuation vs *discontinuation*						
Constant	10.56	3.61	8.54	.0035		
Epidemiology	−0.21	0.10	4.53	.0334	0.81	0.67–0.98
Pathogenesis	0.03	0.05	0.31	.5796	1.03	0.93-1.14
Clinical symptoms	−0.10	0.10	1.41	.2358	0.90	0.76-1.07
Prevention	−0.26	0.19	1.93	.1644	0.77	0.53-1.11
Modification vs *no modification*						
Constant	11.96	3.92	9.30	.0023		
Epidemiology	−0.14	0.10	2.29	.1302	0.87	0.72-1.04
Pathogenesis	0.03	0.05	0.41	.5212	1.03	0.93–1.14
Clinical symptoms	−0.10	0.10	1.28	.2580	0.90	0.76-1.08
Prevention	−0.62	0.23	7.14	.0075	0.54	0.34-0.85

epidemiology information was a protective factor for biologics discontinuation, while the COVID-19-related information on preventive measures was a protective factor for biologics dosage modification. Furthermore, scholarity level positive correlates with both prevention and epidemiology domains, but inversely correlates with pathogenesis domain. To further confirm, COVID-19 related attitudes to modify/discontinue biologics directly correlated with DLQI, disease duration and inversely with scholarity. In literature both scholarity and educational interventions are capable to increase drug adherence and compliance.[41-43] Recently, guidelines and *vademecum* for patients and dermatologists were produced by the Italian Dermatologists Society (SIDEMAST), however the dermatological world is still discordant on use of biologics during COVID-19 pandemics.[12,13] Furthermore, also during the overwhelming emergency,[44-46] dermatologists should dedicate time to discuss COVID-19 insights with patients undergoing biologics in order to prevent their loss of compliance.

However, the present study is not without any limitation. The major shortcoming is represented by the relatively small sample size employed. Furthermore, the knowledge was limited to pre-pandemic period. It would be interesting to evaluate knowledge of dermatological patients undergoing biologics also in postpandemic period.

5 | CONCLUSION

The knowledge of COVID-19 has a paramount importance in dermatological patients undergoing biologics and dermatologists should promote it. Therapy continuation during COVID-19 emergency seems to strictly depend on the quality of information that patients acquire. Discontinuing or modifying biologic therapy expose patients to the risk of losing response to a drug previously useful.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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