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ORIGINAL ARTICLE

Children with psoriasis and COVID-19: factors associated with an unfavourable COVID-19 course, and the impact of infection on disease progression (Chi-PsoCov registry)

J. Zitouni,[1] A.-C. Bursztejn,[2] A. Belloni Fortina,[3] A. Beauchet,[4] V. Di Lernia,[5] A. Lesiak,[6] J. Thomas,[7] Z. Topkarci,[8] N. Murashkin,[9] P. Brzezinski,[10] T. Torres,[11] A. Chiriac,[12] C. Luca,[13] T. McPherson,[14] M. Akinde,[15] A. Maruani,[16] R. Epishev,[9] H. Vidaurri de la Cruz,[17] P.C. Luna,[18] M. Amy de la Bretêque,[1] A. Lasek,[19] E. Bourrat,[20] M. Bachelerie,[21] S. Mallet,[22] M. Steff,[23] A. Bellissen,[24] I. Neri,[25] E. Zafiriou,[26] J.M.P.A. van den Reek,[27] E. Sonkoly,[28,29,30] S.K. Mahil,[31] C.H. Smith,[31] C. Flohr,[15] H. Bachelez,[32,33] E. Mahé,[1,*]
the Groupe de Recherche sur le Psoriasis (GrPso) of the Société Française de Dermatologie, the Groupe de recherche de la Société Française de Dermatologie Pédiatrique (GR SFDP), the PsoProtect study group, the British Society of Paediatric Dermatology (BPSD), and the Società Italiana di Dermatologia Pediatrica (S.I.Der.P.)

[1]Department of Dermatology, Hôpital Victor Dupouy, Argenteuil, France
[2]Department of Dermatology, Hôpitaux de Brabois, Centre Hospitalier Universitaire de Nancy, Vandœuvre-lès-Nancy, France
[3]Pediatric Dermatology Unit, Department of Medicine DIMED, University of Padova, Padova, Italy
[4]Department of Public Health, Hôpital Ambroise Paré, Boulogne-Billancourt, France
[5]Dermatology Unit, Arcispedale S. Maria Nuova, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[6]Department of Dermatology, Peadiatric Dermatology and Oncology, Medical Univeristy of Lodz, Lodz, Poland
[7]J. T. Skin Care Centre, Chennai, Tamil Nadu, India
[8]Department of Dermatology, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[9]Department of Dermatology, Federal State Autonomous Institution, Scientific Center of Children's Health of the Ministry of Health of the Russian Federation, Moscow, Russia
[10]Department of Dermatology, Voivodship Specialist Hospital in Slupsk, Ustka, Poland
[11]Department of Dermatology, Centro Hospitalar Universitário do Porto, Porto, Portugal
[12]Department of Dermatology, Nicolina Medical Center, P. Poni Institute of Macromolecular Chemistry, Romanian Academy, Iași, Romania
[13]Infectious Disease Department, "Sf. Parascheva" Clinical Hospital, "Gr. T. Popa" University of Medicine, Iasi, Romania
[14]Department of Dermatology, Oxford University Hospitals NHS Trust, Oxford, UK
[15]Department of Paediatric Dermatology, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[16]Unit of Pediatric Dermatology, Department of Dermatology, University of Tours and Nantes, INSERM 1246 SPHERE - CHRU Tours, Tours, France
[17]Servicio de Dermatología Pediátrica, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud, Ciudad de México, Mexico
[18]Department of Dermatology, Hospital Alemán, Ciudad Autónoma de Buenos Aires, Argentina
[19]Department of Dermatology, Hôpital Saint Vincent de Paul, Université Catholique de Lille, Lille, France
[20]Department of Dermatology, Hôpital Robert Debré, AP-HP, Paris, France
[21]Department of Dermatology,Centre Hospitalier Universitaire, Clermont-Ferrand, France
[22]Department of Dermatology, Hôpital de la Timone, Assistance-publique-Hôpitaux de Marseille, Marseille, France
[23]Department of Dermatology,Centre Hospitalier Intercommunal Robert Ballanger, Aulnay-sous-Bois, France
[24]Department of Dermatology,Centre Hospitalier Edmond Garcin, Aubagne, France
[25]Department of Dermatology, IRCSS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy
[26]Department of Dermatology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[27]Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands
[28]Dermatology and Venereology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[29]Center for Molecular Medicine (CMM), Karolinska Institutet, Stockholm, Sweden
[30]Dermatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[31]St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK
[32]Department of Dermatology, Hôpital Saint-Louis, AP-HP, Paris, France
[33]Laboratory of Genetic Skin Diseases, INSERM U1163, Imagine Institute, Université de Paris, Paris, France
Correspondence: E. Mahé. **E-mail:** emmanuel.mahe@ch-argenteuil.fr

Abstract

Background The COVID-19 pandemic has raised questions regarding the management of chronic skin diseases, especially in patients on systemic treatments. Data concerning the use of biologics in adults with psoriasis are reassuring, but data specific to children are missing. Moreover, COVID-19 could impact the course of psoriasis in children.

Objectives The aim of this study was therefore to assess the impact of COVID-19 on the psoriasis of children, and the severity of the infection in relation to systemic treatments.

Methods We set up an international registry of paediatric psoriasis patients. Children were included if they were under 18 years of age, had a history of psoriasis, or developed it within 1 month of COVID-19 and had COVID-19 with or without symptoms.

Results One hundred and twenty episodes of COVID-19 in 117 children (mean age: 12.4 years) were reported. The main clinical form of psoriasis was plaque type (69.4%). Most children were without systemic treatment (54.2%); 33 (28.3%) were on biologic therapies, and 24 (20%) on non-biologic systemic drugs. COVID-19 was confirmed in 106 children (88.3%) and 3 children had two COVID-19 infections each. COVID-19 was symptomatic for 75 children (62.5%) with a mean duration of 6.5 days, significantly longer for children on non-biologic systemic treatments ($P = 0.02$) and without systemic treatment ($P = 0.006$) when compared with children on biologics. The six children who required hospitalization were more frequently under non-biologic systemic treatment when compared with the other children ($P = 0.01$), and particularly under methotrexate ($P = 0.03$). After COVID-19, the psoriasis worsened in 17 cases (15.2%). Nine children (8%) developed a psoriasis in the month following COVID-19, mainly a guttate form ($P = 0.01$).

Discussion Biologics appear to be safe with no increased risk of severe form of COVID-19 in children with psoriasis. COVID-19 was responsible for the development of psoriasis or the worsening of a known psoriasis for some children.

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Conflict of interest

V. Di Lernia has undertaken activities as a paid consultant, advisor or speaker for AbbVie, Janssen Cilag, Novartis and Sanofi. A. Lesiak has undertaken activities as a paid consultant, advisor or speaker for AbbVie, Almirall, Janssen Cilag, Leo Pharma, Lilly, Novartis, Pfizer, Sandoz and Pierre-Fabre. N. Murashkin has undertaken activities as a paid consultant, advisor or speaker for Jansen Cilag, Eli Lilly, Novartis, AbbVie, Amryt Pharma, Pfizer, Celgene, Mölnlycke Health Care AB, Zeldis Pharma, Galderma and Bayer. T. Torres has undertaken activities as a paid consultant, advisor or speaker for AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, Samsung-Bioepis, Sandoz and Sanofi. T. McPherson has undertaken paid speaker fees for AbbVie, Leo pharma and Sanofi. R. Epishev has undertaken activities as a paid consultant, advisor or speaker for Eli Lilly, Novartis, AbbVie, Amryt Pharma, Janssen, Pfizer, Celgene and Mölnlycke Health Care AB. I. Neri has undertaken activities as a paid consultant, advisor or speaker for Janssen Cilag, Sanofi and Lilly. J M.P.A. van den Reek carried out clinical trials for AbbVie, Celgene and Janssen and has received speaking fees/attended advisory boards from AbbVie, Janssen, BMS, Almirall, Leo Pharma, Novartis, UCB and Eli Lilly and reimbursement for attending a symposium from Janssen, Pfizer, Celgene and AbbVie. All funding is not personal but goes to the independent research fund of the department of dermatology of Radboudumc Nijmegen, the Netherlands. E. Sonkoly has undertaken activities as a paid consultant, advisor or speaker for Eli Lilly, AbbVie, Janssen Cilag, Leo Pharma, Bristol Myers Squibb, Novartis and UCB. S.K. Mahil has received departmental funding from AbbVie, Celgene, Eli Lilly, Janssen-Cilag, Novartis, Sanofi and UCB. C. Smith has received departmental research funding from AbbVie, Novartis, Pfizer and Sanofi and has served as an investigator on Medical Research Council – and Horizon 2020 – funded consortia with industry partners (see psort.org.uk and biomap – imi.eu). C. Flohr is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principle Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). He also leads the EU Trans-Foods consortium. His department has received funding from Sanofi-Genzyme for skin microbiome work. H. Bachelez has undertaken activities as a paid consultant, advisor or speaker for AbbVie, Almirall, Anaptysbio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Kyowa Kirin, Janssen Cilag, Leo Pharma, Lilly, Novartis, UCB and received research funding support from Boehringer Ingelheim, Bristol Myers Squibb, Leo Pharma, Novartis and Pfizer. E. Mahé has undertaken activities as a paid consultant, advisor or speaker for AbbVie, Amgen, Celgene, Janssen Cilag, Leo Pharma, Lilly, Novartis and Sanofi. Other authors have no conflicts of interest to disclose.

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Introduction

Since the beginning of the SARS-CoV-2 pandemic late in 2019, many questions have been raised about the risk factors of developing severe forms of COVID-19, especially in patients suffering from chronic skin disease on immunomodulators. Systemic drugs used in psoriasis such as biologic therapies, cyclosporine and methotrexate are known to increase susceptibility to infections in adults and children.[1] In the context of uncertainties of this pandemic, both dermatologists and patients are concerned about the safety of continuing or introducing a systemic treatment.

Comorbidities, old age, male sex and non-white ethnicity are the main factors associated with a poorer outcome of COVID-19.[2] There has been lower mortality from COVID-19 in children with a majority of cases asymptomatic or mild, but underlying comorbidities were also linked to poorer COVID-19 outcome in children.[3] Several studies have assessed the risk of poor COVID-19 outcome associated with the use of biologic drugs in inflammatory conditions such as psoriasis, rheumatologic and bowel diseases in adults, and the results are reassuring.[4–7] Some studies have even suggested a protective effect of biologic drugs when compared with systemic non-biologic drugs or no treatment.[5] Those data, reassuring overall, have led to recommend continuation of the systemic treatment when the patient is not infected. However, data are lacking with regard to children with psoriasis under biologic drugs. PsoProtect registry has assessed the course of COVID-19 in patients of all ages with psoriasis. It showed that biologic use in patients with psoriasis was not associated with a higher risk of hospitalization. PsoProtect and other studies only included few paediatric patients and no paediatric-specific subgroup analysis has been performed to date.[4–8]

The impact of COVID-19 infection directly on the course of the psoriasis is also of interest. Viral and bacterial infections are a well-known possible trigger of psoriasis (either psoriasis *de novo*, of exacerbation of psoriasis), particularly guttate psoriasis in children.[9–11] Likewise psoriasis may be exacerbated by SARS-CoV-2.[12–14]

Considering these gaps in the paediatric psoriasis population, we carried out an international study (Chi-PsoCov registry) to assess the severity of COVID-19 in paediatric patients with psoriasis receiving immunosuppressive therapies, and to attempt to investigate the impact of SARS-CoV-2 infection on psoriasis course in the paediatric population.

Material and methods

Study design

Chi-PSoCov, '*CHIldren with PSOriasis and COVID-19*' (www.sfdermato.org/groupe-46-chi-psocov), is a web-based international registry launched on February 1st 2021 and lasting until February 28th 2022. It was developed to evaluate relationship between psoriasis and COVID-19 in children with psoriasis. Real-world observational data were collected using a *Google Forms* case report form. Ethical approval was granted by the 'Comité de protection des personnes – Ouest V – Rennes', in France. Variables in the case report forms were carefully selected to avoid traceability and only anonymized data were submitted. Written consent from patients was therefore not required.

All dermatologists who were members of the French (*Société Française de Dermatologie Pédiatrique*), Italian (*Società Italiana di Dermatologia Pediatrica*), British (*British Society of Paediatric and Adolescent Dermatology*) and European (*European Society of Paediatric Dermatology*) societies of paediatric dermatology, and the French research Group on psoriasis (*Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie*) were invited to participate. A monthly newsletter was sent to all those Societies. Dermatologists who included children with psoriasis in the international PsoProtect registry (psoprotect.org/) were invited to include their children in the Chi-PsoCov registry.

Inclusion criteria

Children were included if (i) they were under 18 years of age at the first symptom, or at diagnosis of COVID-19; (ii) had a history of psoriasis confirmed by a dermatologist before COVID-19, or if they developed psoriasis during the month after the infection with SARS-CoV-2 (definition of *de novo psoriasis*); (iii) had confirmed or highly suspected COVID-19 with or without symptoms. Highly suspected cases were included if (i) characteristic symptoms were present in the subject but not confirmed by testing (especially before the launch of systematic testing procedures), with (ii) identified COVID-19 case in the family household; suspected cases were also included if they were contact cases (in school for example) with highly suggestive symptoms.

Data collection

Data from children with psoriasis were collected anonymously. We requested information about children's socio-demographic characteristics and medical history such as gender, age, weight, height and comorbidities. Information on psoriasis included the age of onset, family history, psoriasis phenotype, nail and articular involvement, severity scores with the Psoriasis Assessment Severity Index (PASI) and the Physician Global Assessment (PGA), as well as current treatments. We collected data on the evolution of the psoriasis after COVID-19 infection, namely worsening or a change in phenotype and the continuation or discontinuation of psoriasis treatments or a change of posology (whether it was reduced or increased). COVID-19 infection

characteristics collected were whether the infection was confirmed (PCR, serology, antigenic test or chest CT-scan) or highly suspected, types and duration of symptoms if symptomatic, child hospitalization, and if the child developed a chronic form of COVID-19 (long COVID-19).

Definitions

Children receiving no systemic treatments were without any treatment or on topical treatments, or phototherapy.

To take into account variations by age, gender and geographic origin for definition of overweight and obesity in childhood, we used the international definition proposed by Cole *et al.*[15]

There was no question regarding recurrences (new flares of COVID-19) in the case report form, so identification of those cases was based on declarations by investigators at the final question in the case report form (open question for any comments). We also checked hospital records to avoid duplicate data entry through different clinicians.

Outcomes

The primary aims of the Chi-PsoCov registry were: (i) to evaluate the effects that different systemic immunomodulatory psoriasis treatments have on COVID-19 outcomes. We analysed groups of treatments: without systemic treatments vs. non-biologic systemic treatments vs. biologic treatments; then we compared the three main groups of treatments (> 10 cases): methotrexate vs. TNF-alpha inhibitors vs. ustekinumab; (ii) to assess the impact of COVID-19 on psoriasis, and on treatment maintenance.

Statistical analysis

Demographic and clinical characteristics and COVID-19 outcomes of the study population were summarized using descriptive statistics. Rates of categorical COVID-19 outcomes in different treatment groups were compared using chi-square test or Fisher test when necessary. Quantitative outcomes were compared using Student's *t*-test. A *P*-value below 0.05 was considered statistically significant. Only *P*-values below 0.05 are given in superscript in tables. Due to the relatively small number of participants, no multivariate study was conducted.

Results

Socio-demographic and clinical characteristics

One hundred and seventeen children were included, with a total of 120 COVID-19 cases reported from 14 countries (France, $n = 62$; Poland, $n = 13$; Italy, $n = 12$; Russia, $n = 6$; United Kingdom and Turkey, $n = 5$; India, $n = 4$; Portugal and Romania, $n = 3$; Argentina and Mexico, $n = 2$; Sweden, the Netherlands, and Greece, $n = 1$ each). Three children had two COVID-19 infection episodes. Clinical and socio-demographic data are detailed in Table 1. Fifty-eight children (49.6%) were female; the mean age was 12.4 ± 3.8 years. Children without systemic treatment were younger ($P = 0.001$), and among children receiving biologics, those treated with ustekinumab were older than those under TNF alpha inhibitors ($P = 0.03$). Nineteen children (16.8%) were overweight and 8 (7.1%) suffered from obesity.

Concerning psoriasis characteristics, the mean age of onset was 7.2 ± 4.0 years. The most frequent psoriasis phenotypes before COVID-19 were generalized plaque psoriasis (69.4%), palmoplantar plaque psoriasis (13%), scalp psoriasis (6.5%) and guttate psoriasis (4.6%). Nail involvement was reported in 44.3%, and psoriasis arthritis in 5.8% of children. Children with psoriasis arthritis were more frequently under biologic therapies than without any systemic treatment ($P = 0.01$). The psoriasis was active before the infection for 82 children (70.1%), and in remission with or without treatment for 26 (22.2%). It was more frequently active for children receiving no systemic treatment (75%) compared to those under non-biologic systemic treatment (57.9%, $P = 0.04$). Remission (no lesion at inclusion) was more frequent among children under biologic therapies (32.4%, $P = 0.02$) and children under non-biologic systemic treatments (42.1%, $P = 0.01$) compared with those without any systemic treatment (3.1%). The mean PGA, PASI and BSA scores before the infection were 1.7, 3.7 and 7.1%, respectively.

A majority of children did not receive any systemic treatments (54.2%) at the time of SARS-CoV-2 infection (Table 1). Systemic treatments at the time of COVID-19 reported were mainly biologic drugs (28.3%). Three treatments were received by more than 10 children: methotrexate ($n = 14$), TNF-alpha inhibitors ($n = 18$) and ustekinumab ($n = 14$).

COVID-19 outcomes

COVID-19 characteristics are shown in Table 2. The infection was confirmed in 106 cases (88.3%) and suspected in the 14 others (11.7%). The infection was symptomatic in most cases (62.5%). The mean duration of symptoms was 6.5 days. This duration was shorter for patients under biologic therapies compared with children under non-biologic systemic treatments (4.3 days vs. 6.9 days, $P = 0.02$) or without treatments (4.3 days vs. 7.7 days, $P = 0.006$); it was also shorter for patients under TNF-alpha inhibitors (4.4 days vs. 7.8 days, $P = 0.04$) or ustekinumab (3.9 days vs. 7.8 days, $P = 0.004$) compared to children under methotrexate.

The three more commonly reported COVID-19 symptoms were fever (62.7%), fatigue (40%) and headache (38.7%). Two children (1.7%) had long COVID-19. No child developed paediatric inflammatory multisystem syndrome (PIMS). Six children (5%) were hospitalized, including one in an intensive care unit.

Of note, overweight and obesity were not associated to symptomatic form, duration of symptoms or to severity (hospitalization) of COVID-19.

Table 1 Demographic and clinical characteristics of 117 children with psoriasis who developed 120 COVID-19 infections

	All patients	Patients receiving no systemic agent	Patients receiving non-biologic systemic therapies†		Patients receiving biologic therapies‡			Missing
			All patients	Methotrexate	All patients	TNF alpha inhibitors	Ustekinumab	
Number of cases	117	63	21	14	33	18	13	
Number of COVID-19	120	65	21	14	34	18	14	
Demographic characteristics								
Gender, female, *n* (%)	58 (49.6)	31 (49.2)	9 (42.9)	5 (35.7)	18 (54.5)	12 (66.7)	5 (38.5)	0
Age (year), mean ± SD	12.4 ± 3.8	11.4 ± 3.9	13.5 ± 3.3§	14.0 ± 3.0	13.8 ± 3.1§	12.9 ± 3.6¶	15.2 ± 2.2¶	0
Body mass index (kg/m^2), mean ± SD	20.5 ± 4.2	19.7 ± 3.5	21.4 ± 4.6	20.3 ± 4.0	21.7 ± 4.9	21.9 ± 4.0	21.8 ± 6.3	4
Overweight, *n* (%)	19 (16.8)	9 (14.5)	4 (21.1)	1 (8.3)	6 (18.8)	5 (31.3)	1 (7.1)	
Obesity, *n* (%)	8 (7.1)	5 (8.1)	2 (10.5)	1 (8.3)	1 (3.1)	0	1 (7.1)	
Psoriasis								
Age at onset (year), mean ± SD	7.2 ± 4.0	6.8 ± 4.1	7.7 ± 4.4	8.4 ± 4.7	7.5 ± 3.8	7.0 ± 3.3	9.2 ± 3.5	0
Family history of psoriasis, *n* (%)	42 (41.6)	23 (40.4)	10 (55.6)	7 (58.3)	9 (34.6)	5 (38.5)	3 (27.3)	13
Phenotype (before COVID)††								0
Plaque psoriasis	75 (69.4)	34 (63.0)	16 (76.2)	11 (78.6)	25 (75.8)	14 (77.8)	11 (84.6)	
Palmoplantar plaque psoriasis	14 (13.0)	6 (11.1)	3 (14.3)	2 (14.3)	5 (15.2)	3 (16.7)	1 (7.7)	
Scalp psoriasis	7 (6.5)	6 (11.1)	0	0	1 (3.0)	0	1 (7.7)	
Guttate psoriasis	5 (4.6)	3 (5.6)	1 (4.8)	1 (7.1)	1 (3.0)	1 (5.6)	0	
Inverse psoriasis	2 (1.9)	2 (3.7)	0	0	0	0	0	
Generalised pustular psoriasis	2 (1.9)	1 (1.9)	1 (4.8)	0	0	0	0	
Erythroderma	2 (1.9)	1 (1.9)	0	0	1 (3.0)	0	0	
Nail psoriasis	1 (0.9)	1 (1.9)	0	0	0	0	0	
Nail involvement, *n* (%)††	51 (44.3)	30 (50.0)	7 (43.8)	5 (41.7)	14 (48.3)	3 (23.1)	9 (69.2)	3
Psoriasis arthritis, *n* (%)††	7 (5.8)	1 (1.5)‡‡	0	0	6 (17.6)‡‡	2 (11.1)	3 (23.1)	3
Psoriasis before COVID, *n* (%)††								3
Active	82 (70.1)	48 (75.0)§§	11 (57.9)§§	8 (66.7)	23 (67.6)	11 (61.1)	10 (71.4)	
In remission with treatment	21 (17.9)	2 (3.1)¶¶	8 (42.1)¶¶	4 (33.3)	11 (32.4)¶¶	7 (38.9)	4 (28.6)	
In remission without treatment	5 (4.3)	5 (7.8)¶¶	–	–	–	–	–	
No psoriasis (*de novo* psoriasis)	9 (7.7)	–	–	–	–	–	–	
Last value before COVID†††††								
PGA, mean ± SD	1.7 ± 1.4	2.1 ± 1.4	1.3 ± 1.3	1.6 ± 1.5	1.3 ± 1.4	0.8 ± 1.3	1.8 ± 1.2	23
PASI, mean ± SD	3.7 ± 6.1	4.0 ± 5.8	3.3 ± 5.5	2.4 ± 3.1	3.3 ± 7.0	3.6 ± 8.7	3.0 ± 4.7	23
BSA, mean ± SD	7.1 ± 15.5	7.3 ± 15.1	6.1 ± 10.3	7.5 ± 13.1	7.4 ± 18.6	11.0 ± 24.5	2.6 ± 3.3	15
Treatment at the time of SARS-CoV-2 infection								
Phototherapy	6 (5.0)	5 (7.7)	0		1 (2.9)	0	1 (7.1)	
Non-biologic systemic therapies†	24 (20.0)	–	21 (100)		3 (8.8)	1 (5.6)	1 (7.1)	
Methotrexate	15 (12.5)	–	14 (66.7)		1 (2.9)	0	1 (7.1)	
Acitretin	7 (5.8)	–	5 (23.8)		2 (5.9)	1 (5.6)	0	
Biologic therapies‡	33 (28.3)	–	0	0	34 (100)	18 (100)	14 (100)	
TNF-alpha inhibitors	18 (15.0)	–	–	–	18 (52.9)	18 (100)	–	
Anti-IL12/23	14 (11.7)	–	–	–	14 (41.2)	–	14 (100)	
Anti-IL17	1 (0.8)	–	–	–	1 (2.9)	–	–	
Anti-IL23	1 (0.8)	–	–	–	1 (2.9)	–	–	

SD, standard deviation.
†Non-biologic systemic therapies were: methotrexate (*n* = 14), acitretin (*n* = 6), apremilast (*n* = 1) and cyclosporine (*n* = 1).
‡Biologic therapies were: TNF alpha inhibitors: adalimumab (*n* = 14), etanercept (*n* = 4); ustekinumab (*n* = 14); secukinumab (*n* = 1) and risankizumab (*n* = 1).
§Age at inclusion: *P* = 0.001 comparing patients receiving no systemic treatment and biologic therapies; *P* = 0.02 comparing patients without systemic treatments and on biologic therapies.
¶Age at inclusion: *P* = 0.03 comparing patients on ustekinumab and on TNF-alpha inhibitors.
††Children with *de novo* psoriasis are not included herein.
‡‡Psoriasis arthritis: *P* = 0.01 comparing patients receiving no systemic treatment and on biologic therapies.
§§Active psoriasis before COVID: *P* = 0.04 comparing patients receiving no systemic treatment and receiving non-biologic systemic treatment.
¶¶Psoriasis in remission (with or without treatment): *P* = 0.01 comparing patients receiving no systemic treatment and receiving non-biologic systemic treatments; *P* = 0.02 comparing patients receiving no systemic treatment and on biologic therapies.
†††Only evaluated for generalized and localised plaque psoriasis (scalp, palmoplantar for example).

Table 2 COVID-19 outcomes in children with psoriasis

	All patients (*n* = 117/120)†	Patients receiving no systemic agent (*n* = 63/65)†	Patients receiving non-biologic systemic therapies		Patients receiving biologic therapies			Missing
			All patients (*n* = 21/21)†	Methotrexate (*n* = 14/14)†	All patients (*n* = 33/34)†	TNF alpha inhibitors (*n* = 18/18)†	Anti-Il12/23 (Ustekinumab) (*n* = 13/14)†	
Covid-19 diagnosis, *n* (%)								0
Confirmed	106 (88.3)	55 (84.6)	19 (90.5)	12 (85.7)	32 (94.1)	16 (88.9)	14 (100)	
Suspected	14 (11.7)	10 (15.4)	2 (9.5)	2 (14.3)	2 (5.9)	2 (11.1)	0	
Close contacts diagnosed with COVID-19, *n* (%)	94 (80.3)	51 (79.7)	15 (78.9)	9 (75.0)	28 (82.3)	16 (88.9)	11 (78.6)	3
N° of COVID-19 infections, *n* (%)								0
1	114 (97.4)	61 (96.8)	21 (100)	14 (100)	33 (97.1)	18 (100)	13 (92.9)	
2	3 (2.6)	2 (3.2)	0	0	1 (2.9)	0	1 (7.1)	
Clinical aspect, *n* (%)								0
Asymptomatic	45 (37.5)	28 (43.1)	5 (23.8)	2 (14.3)	12 (35.3)	9 (50.0)	3 (21.4)	
Symptoms	75 (62.5)	37 (56.9)	16 (76.2)	12 (75.7)	22 (64.7)	9 (50.0)	11 (78.6)	
Hospitalization, *n* (%)	6 (5.0)	2 (3.1)	4 (19.0)	3 (21.4)	0	0	0	0
Evolution								
N° of days of symptoms, mean ± SD	6.5 ± 5.1	7.7 ± 6.2‡	6.9 ± 3.1‡	7.8 ± 3.0§	4.3 ± 2.9‡	4.4 ± 3.6§	3.9 ± 2.5	0
Long COVID, *n* (%)	2 (1.7)	2 (3.1)	0	0	0	0	0	0
COVID-19 symptoms (% among symptomatic cases), *n* (%)¶								0
Fever	47 (62.7)	25 (67.6)	12 (75.0)	8 (66.7)	10 (45.5)	4 (44.4)	5 (45.5)	
Fatigue	30 (40.0)	15 (40.5)	6 (37.5)	5 (41.7)	9 (40.9)	3 (33.3)	5 (45.5)	
Headache	29 (38.7)	14 (37.8)	7 (43.8)	5 (41.7)	8 (36.4)	1 (11.1)	6 (54.5)	
Myalgia	27 (36.0)	13 (35.1)	6 (37.5)	6 (50.0)	8 (36.4)	6 (66.7)	1 (9.1)	
Anosmia	24 (32.0)	13 (35.1)	5 (31.3)	3 (25.0)	6 (27.3)	2 (22.2)	4 (36.4)	
Dry continuous cough	23 (30.7)	12 (32.4)	7 (43.8)	5 (41.7)	4 (18.2)	1 (11.1)	2 (18.2)	
Rhinorrhea	23 (30.7)	11 (29.7)	6 (37.5)	5 (41.7)	4 (18.2)	0	5 (45.5)	
Dysgeusia	15 (20.0)	10 (27.0)	2 (12.5)	2 (16.7)	3 (13.6)	1 (11.1)	2 (18.2)	
Sore throat	15 (20.0)	7 (18.9)	4 (25.0)	4 (33.3)	4 (18.2)	1 (11.1)	2 (18.2)	
Arthralgia	12 (16.0)	7 (18.9)	1 (6.3)	1 (8.3)	4 (18.2)	1 (11.1)	2 (18.2)	
Abdominal pain	11 (14.7)	5 (13.5)	2 (12.5)	1 (8.3)	4 (18.2)	1 (11.1)	3 (27.3)	

SD, standard deviation.
†Children/cases of COVID-19.
‡Duration of symptoms: $P = 0.006$ comparing patients receiving no systemic treatment and on biologic therapies; $P = 0.02$ comparing patients on non-biologic systemic treatment and on biologic therapies.
§Duration of symptoms: $P = 0.04$ comparing patients on methotrexate and on TNF-alpha inhibitors; $P = 0.004$ comparing patients on methotrexate and on ustekinumab.
¶Only symptoms reported by more than 10% (*n* = 8) of symptomatic children.

Impact of COVID-19 on psoriasis

Data on psoriasis characteristics after the infection are detailed in Table 3. The psoriasis after COVID-19 remained the same for the majority of children (75.9%). It worsened for 17 children (15.2%) with the same phenotype except for one child whose phenotype changed (from plaque to guttate type). Nine children (8%) with no known history of psoriasis developed psoriasis *de novo*.

The systemic psoriasis treatment was mostly maintained at the same dose during the infection (71.2%). Dosing was reduced in 14 children (26.9%) and increased in one child (1.9%) due to severity of psoriasis flare-up.

De novo psoriasis

Nine children developed psoriasis *de novo* (Table 4). They were mostly males (66.7%), with a mean age of 10.3 years. None of children was overweight or obese. SARS-CoV-2 infection was confirmed by formal testing, except for one child (11.1%), symptomatic for 7 children (77.8%), with a mean duration of symptoms of 11.3 days. One of these children required

Table 3 Psoriasis outcome after COVID-19

	All patients (*n* = 117/120)†	Patients receiving no systemic agent (*n* = 63/65)†	Patients receiving non-biologic systemic therapies		Patients receiving biologic therapies			Missing
			All patients (*n* = 21/21)†	Methotrexate (*n* = 14/14)†	All patients (*n* = 33/34)†	TNF alpha inhibitors (*n* = 18/18)†	Anti-Il12/23 (Ustekinumab) (*n* = 13/14)†	
Evolution of psoriasis after COVID-19, *n* (%)								8
Remained same	85 (75.9)	42 (66.7)	15 (88.2)	11 (91.7)	28 (87.5)	14 (82.4)	13 (100)	
Worsened	17 (15.2)	12 (19.0)	2 (11.8)	1 (8.3)	3 (9.4)	2 (11.8)	0	
with same phenotype	16 (14.3)	11 (17.5)	2 (11.8)	1 (8.3)	3 (9.4)	2 (11.8)	0	
phenotype changed	1 (0.9)	1 (1.6)	0	0	0	0	0	
Psoriasis *de novo*	9 (8.0)	NA	NA	NA	NA	NA	NA	
Improved	1 (0.9)	0	0	0	1 (3.2)	1 (6.3)	0	
Treatment during COVID-19 among children on systemic therapy, *n* (%)								3
Maintained at the same dosage	37 (71.2)	NA	12 (66.7)	7 (58.3)	25 (73.5)	10 (55.6)	13 (92.9)	
Dose reduced or stopped	14 (26.9)	NA	5 (27.8)	4 (33.3)	9 (26.5)	8 (44.4)	1 (7.1)	
Increased	1 (1.9)	NA	1 (5.6)	1 (8.3)	0	0	0	

NA, not applicable.
†Children/cases of COVID-19.

Table 4 Characteristics of the 9 children who developed psoriasis (psoriasis *de novo*) after COVID-19

	Psoriasis *de novo* (*n* = 9/9)†	Children with history of psoriasis (*n* = 108/111)†
Demographic characteristics		
Sex, female, *n* (%)	3 (33.3)	55 (50.9)
Age (year), mean ± SD	10.3 ± 4.6	12.6 ± 3.6
Body mass index (kg), mean ± SD	18.3 ± 3.0	20.7 ± 4.3
Overweight, *n* (%)	0	19 (18.3)
Obesity, *n* (%)	0	9 (7.7)
Covid-19		
Covid-19 diagnosis, *n* (%)		
Confirmed	8 (88.9)	98 (88.3)
Suspected	1 (11.1)	13 (11.7)
Clinical aspect, *n* (%)		
Asymptomatic	2 (22.2)	43 (38.7)
Symptoms	7 (77.8)	68 (61.3)
Hospitalisation, *n* (%)	1 (11.1)	5 (4.3)
Evolution		
N° of days of symptoms, mean ± SD	11.3 ± 9.3	6.0 ± 4.2
Psoriasis		
Age at onset, mean ± SD	10.3 ± 4.6	7.0 ± 3.9
Familial psoriasis, *n* (%)	6 (75.0)	36 (38.7)
Clinical phenotype after COVID-19, *n* (%)		
Plaque psoriasis	2 (22.2)	75 (69.4)$^{0.01}$
Scalp psoriasis	1 (11.1)	7 (6.5)
Palmoplantar plaque psoriasis	2 (22.2)	14 (13.0)
Guttate psoriasis	3 (33.3)	5 (4.6)$^{0.01}$
Psoriasis arthritis	0	7 (6.3)

SD, standard deviation. In 3rd column, in superscript: *P*-value if <0.05.
†Children/cases of COVID-19.

hospitalization. For 6 of them (75%), a family history of psoriasis was reported. Plaque psoriasis was less frequent ($P = 0.01$) and guttate form more frequent ($P = 0.01$) in comparison with children who already had a known psoriasis before COVID-19. No case of psoriasis arthritis was reported among them.

Hospitalizations

Of the 6 children who required hospitalization (Table 5) for COVID-19, 4 were males (66.7%) and the mean age was 14.2 years. One child was hospitalized in an intensive care unit. There were no reported deaths. Hospitalized children were more frequently on methotrexate (50%, $P = 0.03$), and had an older psoriasis age of onset (10.5% vs. 7 years, $P = 0.01$). No hospitalized child was on a biologic.

Multiple COVID-19 in the same children

Three children had COVID-19 twice. Their characteristics are detailed in Table 6. One of them was taking a systemic treatment (ustekinumab) and was asymptomatic during the two infections. The two others with no systemic treatment were symptomatic at least during the first episode of COVID-19. In children 1 and 3, the COVID-19 was less severe or shorter during the second flare.

Discussion

In this international registry of psoriatic infants, children and adolescents from 14 countries across 3 continents who developed COVID-19, we found no evidence for an increased risk of severe COVID-19 in patients receiving biologic therapies. In symptomatic cases, the duration of COVID-19 symptoms was shorter in children on biologic agents. A potential for more severe forms with methotrexate (three cases hospitalized and longer

Table 5 Characteristics of the 6 children who were hospitalized for COVID-19

	Children hospitalised (*n* = 6/6)†	Asymptomatic and symptomatic children, not hospitalised (*n* = 111/114)†
Demographic characteristics		
Sex, female, *n* (%)	2 (33.3)	56 (50.5)
Age (year), mean ± SD	14.2 ± 3.3	12.4 ± 3.8
Body mass index (kg), mean ± SD	21.5 ± 6.4	20.5 ± 54.2
Overweight, *n* (%)	0	19 (17.3)
Obesity, *n* (%)	1 (33.3)	7 (6.4)
Psoriasis		
Age at onset, mean ± SD	10.5 ± 2.3	7.0 ± 4.0$^{0.01}$
Familial psoriasis, *n* (%)	2 (33.3)	40 (36.0)
Clinical phenotype, *n* (%)		
Plaque psoriasis	5 (83.3)	72 (64.9)
Scalp psoriasis	0	8 (7.2)
Palmoplantar plaque psoriasis	0	16 (14.4)
Guttate psoriasis	1 (16.7)	7 (6.3)
Nail psoriasis	0	1 (0.9)
Inverse psoriasis	0	3 (2.7)
Psoriasis arthritis	0	7 (6.1)
Treatments		
Phototherapy, *n* (%)	1 (16.7)	5 (4.4)
Non-biologic systemic therapies	4 (66.7)	20 (17.5)$^{0.01}$
Methotrexate	3 (50.0)	12 (10.5)$^{0.03}$
Acitretin	1 (16.6)	6 (5.3)
Biologic therapies	0	34 (29.8)
TNF-alpha inhibitors	0	18 (15.8)
Anti-IL12/23	0	14 (12.3)
Anti-IL17	0	1 (0.9)
Anti-IL23	0	1 (0.9)

SD: standard deviation. In 3rd column, in superscript: *P*-value if <0.05.
†Children/cases of COVID-19.

COVID-19) was highlighted. In about one quarter of children (23.2%), there was either an aggravation of existing psoriasis or new onset psoriasis within the month following SARS-CoV-2 infection.

We included cases in 14 countries in Europe, America and Asia, making our findings more generalizable than national studies. However, we have a relatively small number of children limiting the statistical evaluation, and probable inclusion bias. First, children were exclusively seen in hospital setting. It has been shown that children with psoriasis seen in primary care differ from hospitalized children, in part because they have less severe forms of psoriasis and less often receive systemic treatments.[16] Registries that rely on physician-reporting are prone to selection bias, for instance with physicians being more likely to report patients on systemic therapy and with more severe COVID-19. The exposure to different systemic drugs varies accordingly, which limits the assessment of COVID-19 increased severity in the underlying at risk population. Piaserico *et al.* discussed this issue of the so-called floating numerators, which is the lack of reference to the underlying at risk population.[17,18] However international data concerning the prevalence of children under each systemic drug are lacking in hospital setting and private practice, not allowing to compare these proportions. Furthermore, we can also assume that asymptomatic forms of COVID-19 were less likely to be reported by the investigators. So the high frequency of children with systemic therapy in our study (45.8%) does not reflect the standard of care of children. On the other hand, this bias can be considered of interest since the aim of the study was to evaluate impact of systemic treatments on severity of the disease.

The COVID-19 pandemic has raised concerns over the management of immunomodulator treatments in patients, and particularly biologic agents which are known to induce a greater risk of infections. At the start of the COVID-19 pandemic in 2020, recommendations from national and international dermatology societies were to be cautious about initiating biologic therapies in psoriasis patients.[19] In the context of urgency to understand COVID-19, an important number of psoriasis registries (i.e. PsoProtect, PsoProtect-Me, Secure-Psoriasis, but also PsoLar, Psobioteq, ...) have been developed to evaluate links between psoriasis treatments and COVID-19.[20] Only ChiPsoCov focused on children with psoriasis. In a study assessing the quality of the studies evaluating the outcome of patients with psoriasis under biologic drugs, Piaserico *et al.* have found that most of them were biased, and that overall, COVID-19 studies were of poorer quality than other studies. This is in part due to the need for rapid answers in order to manage an emerging disease and its consequences.[17]

A study conducted in France by one of the authors (EM) among psoriatic children during the first lockdown assessed at first hand the impact of the initial lockdown on the disease.[12] That study found a worsening of psoriasis in nearly half the children suffering from the latter, independently of infection ('stress' or treatment stops for example), and it has highlighted the difficulties in complying with preventive measures (e.g. acute increase in psoriasis due to wearing a mask and hand-washing.). The authors also reported that 18.8% of children stopped their systemic treatment, 20% due to medical advice and 10% due to fears of developing severe COVID-19 symptoms.

Most of the published data on the use of psoriasis systemic treatments and COVID-19 outcome concern adults. Mahil *et al.* (PsoProtect registry) have found the same risk factors in adult patients with psoriasis of a poor COVID-19 outcome as in the general population, namely old age, male sex, non-white ethnicity and comorbidities (mainly chronic lung diseases). In their study, patients under biologic drugs were less likely to be hospitalized following COVID-19 than patients taking non-biologic systemic drugs.[5] In another study, Izadi *et al.* gathered the data

Table 6 Children who developed two COVID-19 infections

	Child 1	Child 2	Child 3
Demographic characteristics			
Age at first COVID-19 (year)/gender	8/female	13 / male	12 / female
Body mass index (kg/m^2), (class of weight)	19.5 (overweight)	15.9 (normal)	29.2 (obese)
Comorbidities	No	No	Atopic dermatitis, obesity, sickle cell disease
Psoriasis			
Age at onset (year)	4	8	1
Clinical type	Plaque psoriasis	Plaque psoriasis	Scalp psoriasis
Psoriasis arthritis	No	No	No
First COVID-19			
Date	March 2020	May 2021	March 2020
Systemic treatment (maintained/not)	None	Ustekinumab (maintained)	None
Symptoms	Fever, fatigue, rhinorrhea, headache anosmia, dysgeusia	Asymptomatic	Fever, myalgia, arthralgia, fatigue, dry continuous cough, rhinorrhea, dyspnoea, anosmia, dysgeusia
Duration of symptoms	5 days		15 days
Psoriasis before COVID-19	Active	Active	Active
Evolution of psoriasis after COVID-19	Remained same	Remained same	Remained same
Second COVID-19			
Date	April 2021	January 2022	March 2021
Systemic therapy (maintained/not)	None	Ustekinumab (maintained)	None
Symptoms	Asymptomatic	Asymptomatic	Fever, myalgia, arthralgia, fatigue, dry continuous cough, rhinorrhea, dyspnoea, anosmia, dysgeusia
Duration of symptoms (days)	NA	NA	7 days
Psoriasis before COVID-19	Active	Active	Active
Evolution of psoriasis after COVID-19	Remained same	Remained same	Remained same

NA, not applicable.

of three international registries of patients with immune-mediated inflammatory diseases (rheumatic diseases, inflammatory bowel disease and psoriasis) under systemic treatment.[4] They compared the outcome of COVID-19 regarding the treatment they were taking prior to the infection (TNF-alpha inhibitor monotherapy or combined with methotrexate, or with azathioprine/6-mercaptopurine, methotrexate monotherapy, azathioprine/6-mercaptopurine monotherapy and Janus kinase inhibitor monotherapy). They found a lower risk of poor outcome for patient taking only TNF-alpha inhibitor monotherapy compared to the other monotherapies or combined treatments except for the association of a TNF-alpha inhibitor combined with methotrexate which had an equivalent risk.

A French study assessed the outcome of COVID-19 in adults with psoriasis from the national health insurance database and separately analysed the first and the second waves of the pandemic.[21] It found no difference in mortality between patients taking biologic vs. non-biologic systemic drugs for both waves. They noted an increased risk of hospitalization for patients under non-biologic systemic drugs during the first wave, without increased risk of mortality when compared to patients under biologic drugs. However, this increased risk was not found in the second wave. They concluded that systemic drugs in psoriasis (either biologic or non-biologic drugs) were safe to be continued during the pandemic, but that long-term use of biologic drugs was not associated with a protective effect on SARS-CoV-2 infection. The difference of hospitalization-risk based on the psoriasis treatment between the two first waves may be explained by a change in the patients' behaviour following reassuring data after the first wave and new recommendations on use of biologic therapies. Indeed, it has been reported that patients under biologic drugs were more likely to follow social isolation than patients under non-biologic drugs.[5]

It is not clear if biologic drugs have an actual protective effect on COVID-19 outcome, but data on their use during the pandemic support a non-harmful impact on the course of SARS-CoV-2 infection. These reassuring findings of the use of biologic agents in psoriasis are similar to our findings in children. The severity of COVID-19 has been linked to the cytokine storm syndrome following an excessive stimulation of the immune system.

A high level of serum TNF-alpha in patients infected with SARS-Cov-2 has been linked to a poorer COVID-19 outcome.[22] Thus, the treatment of the disease is based on suppressing this over-activation by the use of corticoids and, in experimental trials, cytokines inhibitors.

Children are less likely than adults to have underlying medical conditions, and have mainly milder forms of COVID-19.[23,24] However some studies have found that children with comorbidities, including obesity, could have a poorer COVID-19 outcome than other children. The role of obesity in severe forms of COVID-19 is subject to debate in paediatrics, but does not seem to have a major impact. Obesity is a known comorbidity associated with psoriasis, even in children.[25–27] Obesity's role in the occurrence of PIMS is not supported.[28–30] In our study, there was no increased risk of COVID-19 severity in obese children with psoriasis. Children who were hospitalized were more frequently on methotrexate than the others.

We also highlighted an effect of COVID-19 on the psoriasis course. Indeed, 6 children developed *de novo* psoriasis in the month following the infection. Interestingly, viral respiratory triggers have been only recently associated with flare-ups of different subtypes of psoriasis, with guttate lesions being one of the most common clinical features in patients with plaque psoriasis.[31] In this latter publication reporting pre-COVID19 pandemic data, the authors identified several respiratory viruses such as metapneumovirus, rhinovirus, influenza and other coronaviruses than SARS-CoV-2. More recently, SARS-CoV-2 infection has been identified to cause severe flare-ups of plaque psoriasis and generalized pustular psoriasis, including a case with IL36RN mutation.[12–14] It therefore seems likely that respiratory viral triggers, including SARS-CoV-2, are responsible for psoriasis flares in susceptible individuals with different genetic backgrounds. Conclusions in our study are limited by the small number of cases, yet we found a higher frequency of guttate form in children developing *de novo* psoriasis than in children with a known history of psoriasis as previously reported in other infections.[10,32] Furthermore, some children had a worsening of their known psoriasis following the infection, and one child had his psoriasis phenotype changed from plaque psoriasis to guttate psoriasis. These findings are consistent with the fact that infectious agents can trigger psoriasis, and SARS-CoV-2 can be listed among them.

Conclusion

In this study, we found no increased risk of a severe form of COVID-19 in children treated with biologic drugs for psoriasis. These data concerning the use of biologic drugs are reassuring and similar to the findings in in the adult psoriasis population. SARS-CoV-2 infection can worsen a previously known psoriasis in some children and induce *de novo* psoriasis. While discussing the initiation or continuation of a systemic treatment, both patients and their families need to be aware of the risk of a psoriasis flare-up in case of infection, and the impact of biologic drugs on the severity of the infection.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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