ORIGINAL ARTICLE

Therapeutic management of adults with atopic dermatitis: comparison with psoriasis and chronic urticaria

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Abstract

Background The therapeutic options in atopic dermatitis rely on consensus-based guidelines, also established for psoriasis and chronic urticaria. However, the therapeutic approach in atopic dermatitis, especially in the moderate-to-severe forms of the disease, seems less aggressive than in psoriasis and in chronic urticaria with a less frequent use of systemic agents.

Objectives To compare in real-life conditions the therapeutic management of adults with atopic dermatitis with those with psoriasis and chronic urticaria.

Methods A transversal analysis was performed in May 2017, using retrospective data from a monocentric database. Data on epidemiology, severity, therapeutic educational intervention and systemic treatments were analysed from 401 patients with atopic dermatitis, compared with data from 230 patients with chronic urticaria and 535 patients with psoriasis.

Results A high proportion (73%) of atopic dermatitis patients presented with a moderate-to-severe form of the disease compared to only 39% of chronic urticaria and 17% of psoriasis patients. Most of atopic dermatitis patients (78%) had completed a therapeutic educational programme, while the adherence was lower in chronic urticaria (35%) and in psoriasis (3%) patients. A systemic treatment, including biologicals, was recorded in 8% of atopic dermatitis patients, while it concerned 26% and 47% of chronic urticaria and psoriasis patients, respectively.

Conclusions We confirmed that atopic dermatitis treatment mostly relies on topical treatments. Only a minority of moderate-to-severe atopic dermatitis patients who are eligible for a systemic treatment receive such therapy. This may suggest promoting a more frequent use of systemic agents in moderate-to-severe atopic dermatitis.

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Conflicts of interest

Dr. Pascal, Dr. Jaulent reports grants from Novartis Pharma S.A.S, during the conduct of the study. Dr. Maucort-Boulch, Dr. Gilibert, Bottigioli, Verdu, Pr. Bérard, Pr. Nicolas have nothing to disclose. Dr. Hacard reports grants from Novartis Pharma SAS, during the conduct of the study. Dr. Nosbaum reports grants from Novartis Pharma S.A.S, during the conduct of the study, other from Novartis Pharma S.A.S, other from Pierre Fabre, personal fees and other from Medac, personal fees and other from AbbVie, personal fees and other from Leo Pharma, personal fees and other from Lilly, grants, personal fees and other from Sanofi-Regeneron, and other from Janssen Cilag, outside the submitted work.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, constantly affecting the quality of life, due to itching, time consumption and sleep disturbance.[1,2] Moderate-to-severe forms of AD affect nearly 50% of patients and are associated with other atopic diseases, like allergic asthma and food allergy.[3] In these cases, the morbidity is important, leading to a considerable economic burden.[4] The first-line treatments of AD are essentially

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based on topical therapy and therapeutic educational programmes (TEP).[5,6]

However, systemic therapy is crucial to control skin inflammation, reduce symptoms, prevent flares and improve quality of life in moderate-to-severe AD patients.[7] The therapeutic options in AD rely on consensus-based guidelines, also established for psoriasis (PSO) and chronic urticaria (CU).[5,6,8-10] Interestingly, the use of systemic agents seems less frequent in AD than in PSO and CU, though the three diseases share common features.[11]

Nowadays, a vigorous approach to disease management is missing in AD. An explanation may be a lower transition definition for starting systemic treatments in PSO and CU than in AD. Indeed, in PSO, a systemic agent can be used for limited disease, defined as 5% body surface area, with a failure of topical treatment.[12] The recent French guidelines on PSO management are even less limiting: the impact on the quality of life matters as much as the severity of the disease.[9] In the same way, CU patients can be switched to biologicals in 4 weeks in the case of antihistamine (AH1) failure.[10] Clinicians themselves also express a high rate of concern about the side-effects of systemic agents, which may delay their prescriptions in AD.[13] However, the recent availability of well-tolerated biologicals, like dupilumab, a human monoclonal antibody against the interleukin-4 receptor alpha, could hasten the AD approach of initiating rapidly and switching between systemic agents when clinical goals are not met.[11]

Given the introduction of new-targeted therapies for AD, recent information on prescribing practices is still sparse.[14,15]

Here, we report on a transversal study, performed in 2017, which compared, in real-life conditions and in an academic setting, the therapeutic management of adults with AD to that of adult PSO and CU patients. Our results show that systemic treatments are under-used in AD patients although they presented with a higher severity score and a worse quality of life than PSO and CU patients. Furthermore, they confirm that treatment of AD is conservative and mostly based on topical agents even in moderate-to-severe forms, which should receive systemic treatments.

Materials and methods

Patients

This transversal study was performed using a database, in which adult patients with a chronic inflammatory skin disease (AD, PSO and CU) were included. They were included by three ways: (i) having at least one medical visit, (ii) having attended a TEP and/or (iii) having attended educative activities lead by the centre, as the National Eczema day or the World Psoriasis Day. Children and patients having been included or being included in clinical trials were excluded. This study was approved by the ethics committee of the Lyon-Sud Hospital.

Data

A database was filled from patients' medical files, and a transversal analysis was performed in June 2017. We collected data on age, sex, age at the disease's onset, medical history, clinical scores, quality of life scores, TEP attendance and treatments. Data concerning the patient's medical history referred to alcohol consumption (current or past, ≥3 doses of alcohol per week), smoking (current or past, ≥1 cigarette per week), cardiovascular risk factor (arterial hypertension, dyslipidaemia, diabetes), cardiovascular disorders (history of myocardial infarction, cerebral vascular accident or arterial ischaemia), neoplasia (history of solid tumour, lymphoma or leukaemia) and body mass index (BMI). The severity of the diseases was defined as the last clinical score recorded in the database. For AD, the European guidelines defined a moderate-to-severe AD by a SCORing Atopic Dermatitis (SCORAD) superior or equal to 25.[5,6] For PSO, when the Psoriasis Severity Index (PASI) was superior to 10, the disease was considered moderate-to-severe.[9] Moderate-to-severe CU was defined as a Urticaria Score Activity (UAS7) between 16 and 42.[16]

Finally, a Dermatology Life Quality Index (DLQI) superior to 10 referred to a significant impact of the chronic disease on the quality of life.[17] Therapeutic data concerned systemic anti-inflammatory treatments commercially available in France, including biologicals but not ultraviolet therapy. Among the systemic treatments, we did not collect data concerning H1-antihistamines (H1A), since H1A represent the first-line treatment of all CU patients.[10]

Biostatistical analysis

Data were extracted in June 2017. Collected variables were described with number and percentage for categorical variables, and mean, range and standard deviation for continuous variables. We focused on comparing the prescribing practices between patients with AD, PSO and CU. Therefore, we used Tukey's range test which is a single-step multiple comparison procedure and statistical test.[18] Statistical comparison of the three groups was performed using the Fisher test for categorical variables and non-parametric analysis of variance (ANOVA) for continuous ones.[19] The level of significance was set at 0.05. Analyses were performed by using the R software.[20]

Results

Patients' characteristics

A total of 1166 patients were included, comprising 401 AD, 535 PSO and 230 CU patients (Table 1). Women represented the majority of AD and CU patients, inversely to PSO. The AD patients exhibited a younger age and a significant earlier disease onset than the PSO and CU patients, as expected for AD which frequently has onset during childhood. More precisely, the mean age at disease onset for AD, PSO and CU was 12.0 ± 18.4,

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Table 1 Clinical and epidemiological data of AD, PSO and CU patients

	AD *N* = 401	PSO *N* = 535	CU *N* = 230	Total *N* = 1116
Gender (%)				
Female	251 (62.6%)	221 (41.3%)	156 (67.8%)	628 (53.9%)
Male	150 (37.4%)	314 (58.7%)	74 (32.2%)	538 (46.1%)
Mean age, years ± SD	37.9 ± 14.9	49 ± 15.1	47.4 ± 15.4	44.9 ± 15.9
Mean age at the disease onset, years ± SD	12 ± 18.4	28.7 ± 16.7	40.3 ± 17.9	25.2 ± 20.4
Medical history (%)				
Alcohol consumption				
Yes	25 (6.2)	71 (13.3)	30 (13)	126 (10.8)
No	21 (5.2)	25 (10.9)	25 (10.9)	125 10.7)
Unknown	355 (88.5)	385 (72)	175 (76.1)	915 (78.5)
Smoking				
Yes	48 (12)	170 (31.8)	34 (14.8)	252 (21.6)
No	104 (25.9)	187 (35)	80 (34.8)	371 (31.8)
Unknown	249 (62.1)	178 (33.3)	116 (50.4)	543 (46.6)
Cardiovascular risk factor				
At least one†	22 (5.5)	157 (29.3)	48 (20.9)	227 (20.3)
Arterial hypertension				
Yes	16 (4)	105 (19.6)	35 (15.2)	156 (13.4)
No	248 (61.8)	299 (55.9)	178 (77.4)	725 (62.2)
Unknown	137 (34.2)	131 (24.5)	17 (7.4)	285 (24.4)
Dyslipidaemia				
Yes	11 (2.7)	87 (16.3)	14 (6.1)	112 (9.6)
No	252 (62.8)	303 (56.6)	197 (85.7)	752 (64.5)
Unknown	138 (34.4)	145 (27.1)	19 (8.3)	302 (25.9)
Diabetes				
Yes	3 (0.7)	44 (8.2)	17 (7.4)	64 (5.5)
No	256 (63.8)	342 (63.9)	195 (84.8)	793 (68)
Unknown	142 (35.4)	149 (27.9)	18 (7.8)	309 (26.5)
Mean BMI ± SD	24 ± 4.6	27.6 ± 5.9	26.6 ± 6	26.6 ± 5.8
Cardiovascular disorders				
Yes	14 (3.5)	46 (8.6)	15 (6.5)	75 (6.4)
No	245 (61.1)	340 (63.6)	196 (85.2)	781 (67)
Unknown	142 (35.4)	149 (27.9)	19 (8.3)	310 (26.6)
Neoplasia				
Yes	14 (3.5)	29 (5.4)	17 (7.4)	60 (5.1)
No	245 (61.1)	365 (68.2)	194 (84.3)	804 (69)
Unknown	142 (35.4)	141 (26.4)	19 (8.3)	302 (25.9)

AD, atopic dermatitis; BMI, body mass index; CU, chronic urticaria; PSO, psoriasis.
†Among arterial hypertension, dyslipidaemia and diabetes.

28.7 ± 16.7 and 40.3 ± 17.9 years, respectively. In terms of medical history, regular alcohol consumption and smoking were significantly found in PSO and in CU patients, compared to AD patients. Notably, alcohol consumption was twice as frequent in PSO and CU than in AD. 31.8% of PSO patients reported a current or past smoking habit, versus 12.0% and 14.8% of AD and CU, respectively. Likewise, more patients with PSO and CU presented at least one cardiovascular risk factor, including arterial hypertension, dyslipidaemia and/or diabetes. According to the BMI, patients with PSO and CU tended to be more overweight than patients with AD. They also presented significantly more cardiovascular disorders, affecting 8.6% of PSO patients and 6.5% of CU patients, while only 3.5% of AD patients had such disorders. A similar trend was seen for the neoplasia rate. Collectively, patients with AD were younger, with an earlier disease onset, but with fewer cardiovascular comorbidities than their counterparts with PSO and CU.

Disease severity

Next, the clinical severity of the patients' disease was analysed. We relied on validated scoring systems for each disease and the last score available in each patient's medical file (Table 2).

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Table 2 Clinical severity of AD, PSO and CU patients

	AD	PSO	CU	Total
Mean scores (range) ± SD				
SCORAD (0–103) (*N* = 195)	37.8 ± 20.3	NA	NA	NA
PASI (0–72) (*N* = 373)	NA	6 ± 6.6	NA	NA
UCT (0–16) (*N* = 111)	NA	NA	9.6 ± 4.5	NA
UAS7 (0–42) (*N* = 111)	NA	NA	13.3 ± 11.9	NA
DLQI (0–30)	8.6 ± 6.1	6.8 ± 7.2	6 ± 6.2	7.2 ± 6.8
Data available (%)	238/401 (59.4)	373/535 (69.7)	157/230 (68.3)	768/1166 (65.9)
Disease severity (%)				
Mild	53 (27.2)	310 (83.1)	61 (61)	424 (63.5)
Moderate-to-severe	142 (72.8)	63 (16.9)	39 (39)	244 (36.5)
Data available	195/401 (48.6)	373/535 (69.7)	100/230 (43.5)	668/1166 (57.3)

AD, atopic dermatitis; CU, chronic urticaria; DLQI, Dermatology Life Quality Index; NA, not applicable; PASI, Psoriasis Severity Index; PSO, psoriasis; SCORAD, SCORing Atopic Dermatitis; UAS7, Urticaria Activity Score; UCT, Urticaria Control Test.

Table 3 Therapeutic intervention in AD, PSO and CU

	AD *N* = 401	PSO *N* = 535	CU *N* = 230	Total *N* = 1166
TEP programme (%)				
Yes	314 (78.3)	15 (2.8)	79 (34.3)	408 (35)
No	87 (21.7)	520 (97.2)	151 (65.7)	758 (65)
Systemic treatments (%)				
Yes	33 (8.2)	249 (46.5)	59 (25.7)	341 (29.2)
No	368 (91.7)	286 (53.5)	171 (74.3)	825 (70.8)
Systemic conventional treatments† (%)				
Acitretin	0	16 (3)	0	16 (1.4)
Apremilast	0	14 (2.6)	0	14 (1.2)
Cs A	3 (0.7)	1 (0.2)	0	4 (0.3)
Dipyridamole	0	0	1 (0.4)	1 (0.1)
Montelukast	0	0	6 (2.6)	6 (0.5)
MTX	27 (6.7)	88 (16.4)	0	115 (9.9)
Biologicals (%)				
Yes	3 (0.7)	130 (24.3)	52 (22.6)	166 (14.2)
No	398 (99.3)	424 (79.5)	178 (77.4)	1000 (85.8)

AD, atopic dermatitis; CsA, cyclosporine A; CU, chronic urticaria; MTX, methotrexate; PSO, psoriasis; TEP, therapeutic educational programmes.
†AntiH1 not included.

The mean SCORAD was 37.8 ± 30.3 for AD patients, and the mean PASI was 6 ± 6.6 for PSO patients. For CU, two scores were available: the UAS7, evaluating the severity of the CU symptoms, and the UCT, used for measuring the impact of CU treatment in daily patient management. The mean UAS7 was 13.3 ± 11.9, and the mean UCT was 9.6 ± 4.5.

Then, we analysed the patient's quality of life, using the DLQI rate. The mean DLQI was higher in AD (8.6) than in PSO (6.8) and CU (6). This means that the quality of life of the patients of our AD cohort was more impacted than that of our PSO and CU cohorts. Pooling the clinical scores together, we stratified the cohorts according to disease severity. In AD, 72.8% of patients were moderate-to-severe, while it concerned only 16.9% of PSO patients and 39% of CU patients. Thus, conversely to AD, the vast majority of PSO and CU patients presented with a mild form of their disease.

In summary, patients with AD had a more severe disease and a more important impact on their daily life than patients with PSO and CU, suggesting that the control of AD was not satisfactory.

Therapeutic management

Finally, we focused on therapeutic intervention comparing AD, PSO and CU patients (Table 3). We analysed the rate of participation in TEP programs and the use of systemic agents, involving conventional systemic treatments, as well biologicals. First, the TEP programs were highly followed by 78.2% of AD patients. Only a minority of PSO patients (2.8%) and 34.3% of

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CU patients completed a TEP training. This difference of the adherence to TEP suggested that PSO and CU patients had a less interest in this patient-oriented pedagogy, probably because their clinical symptoms were better controlled by the treatment.

Next, regarding the prescription of systemic drugs for all patients together, 29.2% were treated with a systemic drug, with almost half of them (14.2%) under biologicals. In AD, although 73% (n = 142) of patients in the cohort had a moderate-to-severe form, thus potentially eligible for a systemic treatment, only 8% (n = 33) received such treatment. Methotrexate was the most frequently prescribed molecule (off-label) for 27 patients, while cyclosporine A (CsA, the only conventional immunomodulator with marketing authorization for AD) was given to only three patients. In PSO and CU, the use of systemic treatments was much more common. In PSO, 249 patients (46.5%) were treated with a systemic agent, mainly methotrexate and biologicals, in 16.4% (n = 88) and 21% (n = 111) patients, respectively. In CU, 59 patients (26%) received a systemic treatment, which was a biological in 88% (n = 52) of them. Taking these results together, systemic agents were more than five times more prescribed in PSO than in AD and more than three times in CU than in AD. These results point to a significant under-use of systemic therapies in AD, compared to PSO and CU (P-value < 0.001), the more so since the AD cohort included more moderate-to-severe patients than the PSO and CU cohorts.

Discussion

In the present study, the analysis of AD therapeutic management showed that systemic treatments are under-used, while the AD patients are mostly moderate-to-severe with a high disease's burden. These results show that topical treatments, the default option before systemic therapies, combining emollients and topical anti-inflammatory products, are not sufficient to treat moderate-to-severe AD patients. They are unable to control AD on a daily basis and to induce a long-term remission. The comparison with two other chronic inflammatory skin diseases, PSO and CU, is striking. While AD patients were more severe than PSO and UC, the AD patients received five times less systemic treatments than patients with PSO and three times less than patients with CU. On the other hand, many AD patients participated in a TEP, with a significantly higher adherence than in PSO and CU. These discrepancies highlight different points, although AD, PSO and CU all have a negative impact on patients' quality of life.

Firstly, AD was not until recently considered as a systemic disease, and so was accompanied by a less aggressive approach, unlike PSO and CU. AD is now tightly linked with serious comorbidities that deteriorate health outcomes beyond the cutaneous symptoms. The role of systemic type 2 inflammation in AD is supported by the occurrence of non-cutaneous comorbidities that affect AD patients.[21,22] In particular, AD is associated with allergic disorders representing the 'atopic march',[23] whereas PSO and CU are significantly associated with psoriatic arthritis on the one hand and thyroid autoimmunity on the other.[24,25] Despite a lower rate of cardiovascular risk factors and disorders in our AD cohorts compared with PSO and CU patients, associations with cardiovascular and neuropsychiatric comorbidities, potentially related to systemic inflammation, may also affect patients with AD.[26-30] Thus, recent insights into the systemic nature[31] of AD eclipse the misconception that AD is just a 'skin-deep' condition and will probably impact the AD therapeutic management.[32]

Secondly, the lack of systemic molecules currently licensed for moderate-to-severe AD[33] may also explain the difference in prescription practises between AD, PSO and CU. During the last decade, the therapeutic landscape has been revolutionized for moderate-to-severe PSO and CU. The new agents are mostly targeted biologics or small molecules, with excellent efficacy and safety profiles, which has lowered the threshold of systemic prescription in PSO and CU. The choice of appropriate systemic therapy for PSO may also be driven by the presence of comorbidities.[34,35] Inversely in AD, CsA was the only immunosuppressive agent specifically approved for severe AD from 1993 to 2017 in European Union, when dupilumab, a monoclonal antibody that blocks the IL-4 receptor subunit alpha, was also approved by the European Medicines Agency for moderate-to-severe AD.[36] Our study conducted in 2017 reflects the absence of approved biologics at that time in AD, since only 3/401 (0.7%) AD patients received biologicals. However, the lack of licensed molecules in moderate-to-severe AD has promoted evaluating alternatives to CsA, such as MTX, used for a long time in PSO. Recently, we showed, in a phase III randomized non-inferiority study, that MTX in moderate-to-severe AD was as effective as CsA, when used subcutaneously at 0.3 mg/kg/week, with a better tolerance than CsA.[37,38] Since then, off-label use of MTX has become our first-line therapeutic choice for moderate-to-severe AD patients, as underlined here with the high number of MTX-treated AD patients (27/401, 6.7%) compared to CsA-treated AD patients (3/401, 0.7%). Given the progress in the assessment of conventional systemic drugs in AD, as well the development of powerful new agents targeting AD,[39] we might expect a rapid change in the transition towards systemic drugs for AD patients, as happened in PSO and CU years ago.

Finally, AD, PSO and CU are now regularly grouped together, as chronic inflammatory skin diseases with systemic and high socio-economic impacts. Therefore, we could assume that the AD management algorithm would be close to those of PSO and CU, which is actually far from being the case. It notably differs regarding to the important place of TEP in AD, compared to PSO and CU. In the recent AD European guidelines, TEP is as important as the emollients in the basic treatment, whatever the patient severity, to improve adherence and coping.[5,6,40] Inversely, TEP is currently absent from PSO and CU guidelines, although recent works on TEP have shown promising

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results.[9,10,41,42] This is in line with the inverse trend found in our cohort, between the rate of TEP attendance (high in AD, low in PSO and CU) and the systemic treatment prescriptions (low in AD, high in PSO and CU). However, it was not possible to evaluate the impact of TEP on the prescription of systemic drugs in this transversal study.

Beyond TEP in the respective guidelines of AD, PSO and CU, some of the criteria required to initiate a systemic treatment are more stringent in AD than in PSO and CU. Regarding severity, an immunomodulatory/immunosuppressive therapy should be proposed to moderate-to-severe PSO patients (PASI > 10) and to CU patients unresponsive to high doses of H1A.[9,10] But so far, a systemic therapy is only reserved for severe AD patients (>SCORAD 50).[5,6] The definition of therapeutic goals is also clearly defined in PSO and CU, but still missing in AD. As an example, the therapeutic aims in PSO are to achieve an absolute PASI < 3, a DLQI 0 or 1 and/or a PASI 90 or PASI 100 response. In CU, we aim to control completely the symptoms as safely as possible. Thus, there is a critical need to homogenize the therapeutic guidelines in AD with its PSO and CU counterparts, to standardize and simplify medical practice and patient care.

To conclude, this transversal study conducted in real-life conditions highlights the high proportion of moderate-to-severe AD patients in a university hospital setting, following TEP but undertreated with systemic agents compared to PSO and CU, two other chronic inflammatory skin diseases. The consideration of AD only as a skin disease, the current lack of licensed systemic agents in AD, the fear of side-effects, the limitation of prescription and the discrepancies between the different therapeutic guidelines can probably explain these differences. Capitalizing on these findings, it may encourage: (i) introducing a systemic treatment more proactively for moderate-to-severe AD patients to conform to the guidelines and the therapeutic algorithms established in PSO and CU; and (ii) evaluating prospectively the impact of educational programmes on the prescription of systemic agent.

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