Clinicopathological definition, management and prognostic value of mogamulizumab-associated rash and other cutaneous events: A systematic review

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Abstract

Introduction

Mogamulizumab is a first-in-class IgG1k monoclonal antibody that selectively targets the chemokine receptor type 4 (CCR4), an essential chemotaxis mediator for T-helper (Th) 2 lymphocites, regulatory T cells (Tregs) and cutaneous lymphocyte-associated antigen-positive skin homing cells (1). Malignant cutaneous T-cells, including those in primary cutaneous T-cell lymphoma (CTCL) and adult T-cell leukemia-lympoma (ATLL), are typically of Th2 phenotype and express CCR4 ubiquitously (2); therefore, the targeting of CCR4 by mogamulizumab leads to a therapeutic antitumour effects (3, 4). The drug was first originally approved in Japan for relapsed or refractory CCR4-positive ATLL in 2012 (5). Thereafter, it has received Food and Drug (FDA) authorisation for mycosis fungoides (MF) and Sézary Syndrome (SS) following failure of at least one previous course of systemic therapy on the basis of an international, open-label, randomised controlled phase III trial versus vorinostat (MAVORIC) (6), and now is available in Europe. One of the most common treatment-related side effects observed has been the mogamulizumab-associated rash (MAR), which affects up to a quarter of patients and is the most frequent adverse event leading to drug discontinuation (i.e., 7% of patients in the mogamulizumab group, according to the MAVORIC trial) (6). Since then, the following four predominant clinical patterns have been described in relation to MAR: folliculotropic MF-like scalp plaques with alopecia, papules and/or plaques, photodermatitis, and morbilliform or erythrodermic dermatitis (Fig.1) (7). These clinical entities need to be distinguished from the progression of the underlying disease in order to prevent potentially premature drug discontinuation (8). The development of MAR has been suggested as a possible favorable prognostic factor associated with a significant overall survival benefit in ATLL and greater durable responses in MF/SS (9, 10, 11). According to a recently published consensus of experts in the field, MAR severity can be clinically classified as grade 1 (i.e., macules-papules covering < 10% body surface area – BSA - with or without symptoms), grade 2 (i.e., macules-papules covering 10-30% BSA with or without symptoms, limiting daily activities, rash covering > 30% BSA with or without mild symptoms), and grade 3 (i.e., macules-papules covering > 30% BSA with moderate or severe symptoms, limiting self-care activites of daily living) (12). In terms of histological features, three main patterns have been described: psoriasiform/spongiotic, lichenoid/CD8+ interface, and granulomatous, with mixed patterns often seen (12). As the number of patients treated with mogamulizumab has grown rapidly worldwide, it has become clear that MAR has a more complex spectrum of clinicopathological presentations and other cutaneous events, with clinical and histological features different from the “classic” MAR, have been reported in single-center experiences. Several trials

are currently assessing the efficacy of mogamulizumab in treating advanced or metastatic solid tumors, therephore there is the possiblity that drug will be used in an increasingly number of diseases and broader geographical areas (13-17).

To date, no systematic review on mogamulizumab-associated cutaneous events, including MAR, has been conducted and the current data available are based largely on case reports and case series. The aim of this study is to perform a systematic review of patients diagnosed with MAR and other mogamulizumab-related cutaneous events to identify which are their clinical and histological characteristics, how they are managed in daily practice and whether his development has prognostic implications.

Protocol and registration

The protocol for this review was defined a priori and registered online in the PROSPERO international prospective register of systematic reviews (CRD42023388458). This review was conducted in accordance with PRISMA and the Cochrane Handbook for Systematic Reviews (18).

Eligibility criteria

Studies were included if (i) patients' mogamulizumab-associated cutaneous reactions were diagnosed either clinically, histologically, or both; (ii) the studies were randomized controlled trials, cohort studies, case–control studies, cross-sectional studies, case series, case reports or letters; (iii) the papers were published in the English language and (iv) they reported at least one outcome of treatment. Therapy cycles were defined according to the commonly used schedule (administration of intravenous mogamulizumab, at the dosage of 1.0 mg/kg, on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle) (6). Studies were excluded if (i) a diagnosis of MAR or other mogamulizumab-related cutaneous events was not made; (ii) they were reviews, abstract or poster presentations. No restrictions were set on the number and the age and ethnicity of patients included in a study.

Information sources

The MEDLINE, Embase and Cochrane databases were searched from inception from 10 March 2010 to 2 January 2023 using the only search term 'mogamulizumab'. Restriction to the English language was set. The reference lists of the shortlisted studies were then screened. The PRISMA statement was followed, and the checklist completed.

Study selection

Following the database search, studies were compiled into a single list with all duplicates removed. Titles and abstracts were then screened for initial eligibility by two reviewers independently (G.A.) and (C.A.) and conflicts were resolved by a third independent reviewer (S.A.V.). Full-text publications were retrieved and assessed using the complete

eligibility criteria in a similar fashion. Reference lists of included publications were screened, and citation tracking was completed on Google Scholar. Figure 1 outlines the study selection process (Figure 2).

Outcomes

The primary outcomes measures were (i) clinical and histological characteristics (ii) therapy (iii) response to mogamulizumab regimen defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Secondary outcomes measures were (i) time to skin reaction onset, (ii) number of infusions before onset (iii) duration and (iv) treatment discontinuation.

Data collection, synthesis, and management

Data were extracted independently by two authors (G.A) and (C.A) into a Microsoft Excel spreadsheet. The information extracted from eligible studies included general information (first author's name, year of publication, country), study characteristics (study type, number of patients), participant characteristics (age, sex), lymphoma type (MF/SS, ATLL or others) and primary or secondary outcome measures.

Quality and risk of bias in individual studies

Two reviewers (G.A. and G.T.) assessed the methodological quality of the evidence and the risk of bias of the included studies independently using the 20-item Quality Appraisal Checklist for Case Series Studies, developed by the Institute of Health Economics using the Delphi method (19) (Supplementary Table 1). Any uncertainty was resolved through discussion with a third reviewer (S.A.V.).

Data analyses

All numeric variables were presented with mean and standard deviation (SD), whereas the categorical ones were summarised using absolute frequency and percentage values.

Results

A total of 2073 records were initially identified through a literature search, 843 of which were duplicates. After screening for eligibility and inclusion criteria, 49 articles reporting mogamulizumab-associated cutaneous events were included (6-11, 20-62) (Table 1). Most publications were case reports/letters to the editor (n=28), followed by case series (n=14), original articles (n=6) and clinical trials (n=1). A total of 1516 patients were retrieved, with a slight male prevalence as for the available data (639 males and 570 females, i.e., 52.9% versus 47.1%). Sex distinction of the patients experiencing skin reactions in the different studies was detectable in 462 cases (30.5%) and this cohort

displayed a mean age of 61.5 (SD: 13.73). The most common diseases were ATLL (n=279) and MF/SS (n=124), followed by EBV T-LPD (Epstein-Barr virus-associated T-cell lymphoproliferative diseases) (n=1) and PTL-NOS (peripheral CD4+ T-cell lymphoma, not otherwise specified) (n=1), for a total of 405 patients with analysable information. As for the anatomical distributions of the cutaneous events, the trunk was the most involved site (30.3%), followed by the head/neck (28%), the upper limbs (22.3%), and the lower limbs (20.6%). Response rates to mogamulizumab therapy were reported in 32.6% of the patients, with good outcomes in most of the cases, as complete (CR) and partial (PR) responses accounted for up to 89.4% of the patients whose outcome was clearly specified in the reports. Mogamulizumab-associated cutaneous reactions led to therapy discontinuation in little more than half of the analysed subjects (i.e., 58.8%), with similar trends in both ATLL and MF/SS subsets of patients. Therapy re-start after temporary drug discontinuation was described in 68.8% of the studies. Concerning the clinical presentation of the cutaneous reactions, complete data were accessible in 62.7% of the cases, for a total of 254 patients. The five most common skin reactions were spongiotic/psoriasiform dermatitis (22%), eruptions characterized by the presence of papule and/or plaques (16.1%), cutaneous granulomatosis (11.4%), morbilliform or erythrodermic dermatitis (9.4%), and photodermatitis (7.1%). Folliculotropic–MF-like scalp plaques with alopecia and other alopecia phenomena accounted for the 5.1% and 4.3% of the available cutaneous reactions. Severe forms of cutaneous reactions with systemic symptoms, such as Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN), were reported in three (1.2%) and six cases (2.4%), respectively. Data regarding the management of the cutaneous reactions were available in only 26.9% of the patients, with higher reporting rates in the MF/SS (i.e., 52.4%) compared to the ATLL (i.e., 15.4%) subset of patients. As for the management, the most prescribed treatments were systemic (43.1%) and topical (39.4%) corticosteroids, followed by methotrexate (5.5%). Intravenous immunoglobulins and dupilumab were also mentioned to be useful in few cases (2.8% and 1.8% of the patients, respectively). With regard to the timing of the mogamulizumab-associated cutaneous reaction, very few details were available, as the reporting rates of skin reaction onset, duration, and prior number of infusions were retrievable in only 8.4%, 3.2%, and 11.4% of the analysed patients, respectively. Overall, cutaneous reactions were seen after a mean time of 195.1 days and 9.7 infusions, with an average duration of 161.8 days. Data on T-cell receptor clonality and CD4+/CD8+ ratio in the histopathology report of the MAR were available in ten and eleven studies, respectively, with normal-inverted CD4+/CD8+ ratios in all cases (100%). As for other mogamulizumab-associated cutaneous events, lichenoid reactions, interface dermatitis, vitiligo and generalised eruptive lentiginosis were reported in 5.1%, 5.1%, 1.6%, and 0.8% of the analysed patients, respectively. Other occasional skin findings, encompassing a total of 11.8% patients in the analysed cohort, were facial oedema (5 patients), erythema multiforme (4 patients), mucosal involvement (3 patients), scaling of the scalp (2 patients), cutaneous CD8+ T-cell pseudo-lymphoma (1 patient), ecthyma gangrenosum (1 patient), eruptive sebaceous

hyperplasia (1 patient), unspecific grade 3 skin reaction (1 patient), lupus miliaris disseminated faciei (1 patient), palmo-plantar hyperkeratosis (1 patient), and pustular eruption (1 patient). A further data analysis assessing histological manifestations only, showed as spongiotic/psoriasiform dermatitis represents the most common pattern found (50.5%), followed by granulomatous pattern (26.1%) and interface/lichenoid dermatitis (23.4%). As for the clinical presentation, papules and/or plaques was the most common cutaneous events encountered (28.7%), followed by morbilliform or erythrodermic dermatitis (16.8%), photodermatitis (12.6%), follulotropic-MF like scalp plaques with alopecia (9.1%), alopecia (7.7%), vitiligo (2.8%), generalised eruptive lentiginosis (1.4%). All the other cutaneous presentations together account for the 21% of cases (Supplementary table 2).

Discussion

This systematic review collects the currently available data regarding mogamulizumab-associated cutaneous events in the scientific literature and a multitude of clinical and histopathological presentation of cutaneous adverse reactions events have emerged. Overall, the outlined clinical manifestations appear more frequently of mild-moderate severity and reversable, whilst severe cutaneous reactions, such as SJS and TEN, have been reported only in few cases (9, 35, 38, 41, 42, 54, 60). The manifestation in the same patient of two distinct cutaneous events with different temporal onset is uncommon (46), though the presence of more than one histopathologic pattern in different biopsy specimens has been described (25, 27). The mean age of MAR onset closely depends on the underlying disease, and no data for pediatric patients are available as no juvenile toxicity studies have been conducted so far (1). A key element emerged is the crucial need of a clear distinction between MARs and disease progression, being a misinterpretation one potential reason of incorrect mogamulizumab's effectiveness assessment and unnecessary drug discontinuation (12). From a histological point of view, there are three most frequent patterns of MAR: spongiotic/psoriasiform dermatitis, interface/lichenoid dermatitis, and granulomatous dermatitis. Based on our results, spongiotic/psoriasiform dermatitis represents the most frequent MAR and this is in agreement with what has been previously reported (27). However, these latter findings deserves further considerations. As noted, the coexistence of multiple histologic patterns may represent a not so rare occurrence, with even three pattern described in the same lesions (27). It therefore cannot be excluded that in some studies there has been a description limited to the main histological pattern, whereas investigation aimed at specifically explored the histological aspects could showed a higher degree of descriptive accuracy. Moreover, albeit certain overlapping features founded at histopatological examination of psoriasiform and the spongiotic pattern lead to consider both the patterns together, in same cases they were analysed separately (8,27). Therefore, our results should be interpreted keeping these observations in mind. Beyond the above-mentioned patterns, there are additional and less explored histological features that may variably be helpful in distinguishing MAR from the

progression of the underlying disease, mostly wheter assessed as a whole. Eosinophils are unexpectedly been described as incosistently present in the different studies whereas the presence of a histiocytic component seems to be an additional clue in favor of MAR (8,27). Features mimicking MF/SS such as exocytosis, lymphocytes tagging the dermal-epidermal junction, lamellar fibroplasia and citological atypia are variably represented, focal and of mild intensity. At molecular and immunohistochemical evaluation the following diagnostic clues have been showed to be useful: (i) a decreased CD4:CD8 ratio within intraepidermal lymphocytes, (ii) the lack of T-cell-receptor (TCR) clonality in the skin and blood evaluated by means of high-throughput sequencing analysis of TCR, (iii) the retention of CD7 expression (12). These features strongly favor MAR over recurrent disease (7, 8, 11, 22, 27). As for the putative mechanisms behind the occurrence of MAR, the mogamulizumab-related Treg cells depletion seems to result in an increased activation of CD8+ which presumably targets autoantigens on epidermal keratinocytes (33). Treg cells also regulates the peripheral checkpoint to avoid the autoantibody production: their consequent depletion has been shown to elicit the production of autoantibodies directed again keratinocytes and melanocytes (63,64). As for the mogamulizumab-induced photosensitivity, it remain incompletely elucidated and limited evidence has been provided so far. One of the largest samples analysed were four patients receiving concomitant NB-UVB phototherapy and mogamulizumab and who devoleped erithemato-papular lesions. Phototests found that the minimal erythemal dose was decreased by 20-30mj/cm2 and only one patient also had a low minimal response dose of UVA. Thus, the spectrum of action of mogamulizumab-photosensitivity seems mainly relatable to UVB, and UVA may be additionally involved in certain cases. At histological examination an increased number of CD8+ lymphocytes and fewer Foxp3+ cells were found in the photosensitivity lesion compared with lymphoma (33). Overall, this findings are in line with other published report supporting the involvement of Treg lymphocyte depletion also in the mogamulizumab-induced photosensitivity (43,44). It is yet possible hypotesized that certain UV-modified proteins or UV-induced surface molecules on keratinocytes could be the targets of CD8+ lymphocytes activated as a consequences of drug introduction (33). As stated by several studies speculating on the potential positive role of mogamulizumab-associated cutaneous events and the patients' prognosis, our results showed that the majority of subjects experiencing any skin events achieved a response to mogamulizumab. According to Yonekura *et al*., the tumor infiltrating CD8+ lymphocytes promoted by the reduction of Treg cells are indicative of enhanced antitumour immunity (10). Treatment continuation in cases of biopsy-proven CD8+ lymphocitic lesions following mogamulizumab start has been therephore recommended (9, 10, 35). Similarly, Wang *et al.* highlighted the role of immune modulation mechanisms, including depletion of Treg cells by CCR4 blockade, as triggers of an exaggerated cytotoxic response, which seems accountable for the delayed onset of the rash observed in these patients (27). A higher frequency of MAR appears to be noticeable in SS compared to MF patients, probably due to the different underlying pathophysiology of the two entities (8, 62). As

higher blood disease burden seems to be related to more frequent MAR development and concomitant better overall response, Trum *et al*. speculated that the depletion of both functional immunomodulatory and dysfunctional tumor Tregs in CTCL patients with higher blood disease burden may be associated with greater T-cell dysregulation in peripheral blood and skin (8). As for the findings reported by De Masson *et al.,* skin rashes were again associated with long-term overall survival, along with overexpression of the macrophage-derived CXCL9 and CXCL11 chemokines, recruitment of CD1631 macrophages and reactive CD81 T cells in the skin as well as gradual elimination of the CD41 tumor T-cell clone (62). Similar data emerge from studies focusing on mogamulizumab-induced cutaneous granulomatous eruptions, in which durable clinical responses, most likely secondary to a shift toward an antitumoral Th1 inflammatory milieu, were described (11, 25). Furthermore, increased cytokine Th1 milieu has been considered one of the possible causes of psoriasis recurrences that arose following the introduction of mogamulizumab (44,70). Outside of clinical trials, few cutaneous adverse events have been described so far in patients who received mogamulizumab to treat a lymphoma other than MF/SS or ATLL such as a *malessezia*-driven head and neck dermatitis occurred in a patient with peripheral CD4+ T cell lymphoma [Asokan], a photodermatitis in a patient with EBV T-LPD [Masuda], and a grade II skin event in a patient with refractory/relapsed angioimmunoblastic lymphoma [Oka]. These are only a negligible proportion of cutaneous adverse events that have been encountered, and this is likely due to the rarity and aggressiveness of these forms as well as the few reports describing the use of mogamulizumab in this type of disease (61, 71-77). Little is known about the risk of relapse at the time of drug re-challenge. Few studies reported no recurrence of MAR after therapy rechallenge (8, 25), whilst others described the onset of delayed cutaneous events similar to the first episode of MAR, yet with no life-threatening consequences, suggesting that development of MAR should not preclude future treatment with mogamulizumab (7, 62). Concerning the therapeutic management of MAR by healthcare providers, a relatively high degree of heterogeneity has emerged, especially prior to the 2022 expert consensus recommendations (12). As thoroughly outlined by Musiek *et al*., clinical grading of MAR should guide the proper management (12). Specifically, grade 1 events can be managed without recurring to drug discontinuation nor skin biopsy, with the support of high-potency Class 1 topical steroids and anti-pruritic agents (e.g., antihistamines, or GABA analogs, doxepin, mirtazapine). Conversely, a biopsy should be considered in cases of non-resolving grade 1, and all cases of grade 2 or 3 MARs, to obtain a histopathologic proof of the clinical suspect (12). In the latter two scenarios, in which symptoms tend to be more intense and have an impact on patients' daily life, delaying mogamulizumab and administering oral steroids (0.5 – 1 mg/kg/day) should be considered as first options (12). In our review, topical steroids, systemic steroids, and methotrexate were the most common primary therapeutical strategy used (7, 8, 10, 11, 20-25, 28, 29, 32, 33, 35, 38-43, 44, 46, 47, 49, 51, 52, 54, 57-59, 62). Few patients have been treated with dupilumab, including a case of treatment-refractory MAR in whom a short course of seven dupilumab injections –

preferred over a more protract regimen to minimize any potential risk of CTCL exacerbation – successfully treated the eruption. However, the exact mechanism by means of dupilumab could be effective in the treatment of MARs has not established yet (8, 20). Doxycycline and hydroxychloroquine resulted in no improvement in mogamulizumab-induced granulomatous dermatitis of the scalp (22), whereas azathioprine was a suitable therapeutic option in a case of toxicoderma-like eruption and autoimmune hepatitis (21). Intravenous immunoglobin (IVIg) therapy combined with pulse methylprednisolone achieved complete responses in TEN following mogamulizumab (41, 42, 45).

Limitations

This review encompasses several types of studies, with differences in terms of specialty fields (i.e., hematology vs dermatology), levels of evidence (i.e., single center vs multicenter experiences), and statistical power. Several limitations have emerged across the studies and warrant attention. Firstly, there were remarkable differences in reporting clinical and morphological features of the mogamulizumab-induced cutaneous reactions between the ATL and MF/SS clusters of studies. For instance, anatomical distribution and response rates were reported in 16.5% and 15.1% of the cases in the former group of studies, whilst up to 69.4% and 73.4% in the latter. These findings are likely relatable to a different approach in describing the characteristics of cutaneous reactions and their relationship with disease outcome among different specialists (i.e., hematologists and dermatologists), yet they may be also attributable to the growing attention throughout the years towards mogamulizumab-associated cutaneous events, as the drug has received approval for CTCL few years after ATLL (1, 5). Secondly, most data on MARs occurring in ATLL comes from hematological facilities in Japan, a geographical area where the human T-cell leukemia virus type 1 (HTLV-1) is endemic, the ATLL incidence is estimated to be 1000-1500 per year, and the nationwide estimation of the number HTLV-1 carriers is at least of 1.08 million (65-67). Conversely, data on MARs occurring in CTCLs mainly derive from Northern American and European institutions, areas in which ATLL is significantly less represented (65). Third, the small cohort size, along with the retrospective nature of the studies, poses most case reports at a weak level of scientific evidence, preventing to establish any certain causal relationship between the evaluated cutaneous event and the drug administration. Moreover, the analysed cohorts included patients treated both in clinical trials and in real-life settings, and these populations are known to have different characteristics and outcomes, due to specific inclusion criteria. At last, a thorough assessment of the histologic, immunohistochemical, and clonal features of the cutaneous events, such as CD+/CD8+ ratio, CD7 expression, and T-cell gene rearrangements were rarely reported in the published manuscripts, yet have been recognized as key elements of MAR definition (12). As thoroughly described by Wang and colleagues, the combined use of immunohistochemistry, through the individualization of an inverted or normalized CD4:CD8 ratio within the intraepidermal lymphocytes, and TCR-HTS, which can help the distinction of disease-associated clones with

greater sensitivity and specificity than polymerase chain reaction techniques, are valid tools in distinguishing MAR from CTCL (27, 68, 69). However, considering the costs and the low availability of next generation sequencing in many clinical settings, the authors did not wish to portray TCR-HTS as critical to the routine diagnosis of MAR, but rather as an ancillary study providing further support for the overall clinicopathologic impression (27). The findings of our review are in line with this conclusion, as T-cell clonality of mogamulizumab-induced cutaneous events was rarely assessed in clinical practice and indeed may be unfeasible on a routine basis in most facilities.

Conclusions

The landascape of MAR and other cutaneous events displays heterogenous clinical and histological features. Our results underscore how the majority of the reported cutaneous adverse effects while on mogamulizumab have been mild-to-moderate and still manageable in clinical practice, though caution is always needed and case-by-case management should be adopted. It cannot be excluded that new emerging events will be observed and a better understanding of the characteristics of previous established ones will be possible. Consequently, knowledge of the mogamulizumab-associated MAR and other cutaneous events is likely to be of increasing interest for a larger number of healtcare providers. Albeit Tregs lymphocytes depletion are one of the most frequently involved factors along with an altered disease background, the mechanisms which drive the onset of the adverse events remains unclear. Future research will need to focus on the MAR prognostic implications and to identify genomic and molecular markers for a more rapid and accurate diagnosis.

Table 1: Demographic and clinical characteristics

		ATL (N=279)	EBV T-LPD (N=1)	MF/SS (N=124)	PTL NOS (N=1)	Overall (N=405)
Gender						
n. patients [1]	n (%)	39 (14%)	1 (100%)	95 (76.6%)	1 (100%)	136 (33.6%)
Male	n (%)	22 (56.4%)	1 (100%)	41 (43.2%)	1 (100%)	65 (47.8%)
Female	n (%)	17 (43.6%)	0 (0%)	54 (56.8%)	0 (0%)	71 (52.2%)
Age (total)						
n. patients [1]	n (%)	15 (5.4%)	1 (100%)	11 (8.9%)	1 (100%)	28 (6.9%)
	mean (SD)	68.8 (11.41)	74 (-)	54.7 (16.98)	76 (-)	63.7 (15.2)
Age (Pts skin react.)						
n. patients [1]	n (%)	18 (6.5%)	0 (0%)	18 (14.5%)	1 (100%)	37 (9.1%)
	mean (SD)	64.9 (18.91)	- (-)	57.3 (22.38)	76 (-)	61.5 (13.73)
Skin reaction Onset (days)						
n. patients [1]	n (%)	21 (7.5%)	0 (0%)	12 (9.7%)	1 (100%)	34 (8.4%)
	mean (SD)	120.7 (154.63)	- (-)	236.6 (209.92)	730 (-)	195.1 (211.81)
Duration (days)						
n. patients [1]	n (%)	6 (2.2%)	0 (0%)	6 (4.8%)	1 (100%)	13 (3.2%)
	mean (SD)	87.8 (87.63)	- (-)	230.5 (145.75)	56 (-)	161.8 (138.6)
Infusions before onset						
n. patients [1]	n (%)	36 (12.9%)	0 (0%)	10 (8.1%)	0 (0%)	46 (11.4%)
	mean (SD)	7.6 (3.61)	- (-)	14.9 (14.71)	- (-)	9.7 (10.07)
Anatomical distribution *						
n. patients [1]	n (%)	46 (16.5%)	0 (0%)	86 (69.4%)	1 (100%)	133 (32.8%)
Trunk	n (%)	14 (30.4%)	0 (0%)	39 (45.3%)	0 (0%)	53 (30.3%)
Head/neck	n (%)	8 (17.4%)	0 (0%)	40 (46.5%)	1 (100%)	49 (28%)
Upper limb	n (%)	12 (26.1%)	0 (0%)	27 (31.4%)	0 (0%)	39 (22.3%)
Lower limb	n (%)	12 (26.1%)	0 (0%)	24 (27.9%)	0 (0%)	36 (20.6%)
Overall Response Rate						
n. patients [1]	n (%)	42 (15.1%)	0 (0%)	91 (73.4%)	0 (0%)	132 (32.6%)
CR	n (%)	19 (45.2%)	0 (0%)	41 (45.1%)	0 (0%)	59 (44.7%)
CR+PR	n (%)	15 (35.7%)	0 (0%)	6 (6.6%)	0 (0%)	21 (15.9%)
PR	n (%)	1 (2.4%)	0 (0%)	37 (40.7%)	0 (0%)	38 (28.8%)
SD	n (%)	1 (2.4%)	0 (0%)	3 (3.3%)	0 (0%)	4 (3%)
SD+PD	n (%)	5 (11.9%)	0 (0%)	0 (0%)	0 (0%)	5 (3.8%)
PD	n (%)	1 (2.4%)	0 (0%)	4 (4.4%)	0 (0%)	5 (3.8%)
Treatment Discontinuation						
n. patients [1]	n (%)	13 (4.7%)	0 (0%)	100 (80.6%)	1 (100%)	114 (28.1%)
Yes	n (%)	6 (46.2%)	0 (0%)	61 (61%)	0 (0%)	67 (58.8%)

No	n (%)	7 (53.8%)	0 (0%)	39 (39%)	1 (100%)	47 (41.2%)
Reaction Type						
n. patients [1]	n (%)	28 (10%)	1 (100%)	223 (179.8%)	2 (200%)	254 (62.7%)
spongiotic/psoriasiform dermatitis	n (%)	2 (7.1%)	0 (0%)	54 (24.2%)	0 (0%)	56 (22%)
papules and/or plaques	n (%)	3 (10.7%)	0 (0%)	38 (17%)	0 (0%)	41 (16.1%)
cutaneous granulomatosis	n (%)	0 (0%)	0 (0%)	28 (12.6%)	1 (50%)	29 (11.4%)
morbilliform or erythrodermic dermatitis	n (%)	7 (25%)	0 (0%)	17 (7.6%)	0 (0%)	24 (9.4%)
photodermatitis	n (%)	1 (3.6%)	1 (100%)	16 (7.2%)	0 (0%)	18 (7.1%)
folliculotropic–MF-like scalp plaques with alopecia	n (%)	0 (0%)	0 (0%)	13 (5.8%)	0 (0%)	13 (5.1%)
interface dermatitis	n (%)	2 (7.1%)	0 (0%)	11 (4.9%)	0 (0%)	13 (5.1%)
lichenoid	n (%)	0 (0%)	0 (0%)	12 (5.4%)	1 (50%)	13 (5.1%)
alopecia	n (%)	0 (0%)	0 (0%)	11 (4.9%)	0 (0%)	11 (4.3%)
vitiligo	n (%)	0 (0%)	0 (0%)	4 (1.8%)	0 (0%)	4 (1.6%)
generalised eruptive lentiginosis	n (%)	0 (0%)	0 (0%)	2 (0.9%)	0 (0%)	2 (0.8%)
Others	n (%)	13 (46.4%)	0 (0%)	17 (7.6%)	0 (0%)	30 (11.8%)
TEN [2]	*n (%)*	*6 (46.2%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*6 (20%)*
facial oedema [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*5 (29.4%)*	*0 (0%)*	*5 (16.7%)*
EM [2]	*n (%)*	*4 (30.8%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*4 (13.3%)*
mucosal involvement [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*3 (17.6%)*	*0 (0%)*	*3 (10%)*
SJS [2]	*n (%)*	*3 (23.1%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*3 (10%)*
scaling of the scalp [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*2 (11.8%)*	*0 (0%)*	*2 (6.7%)*
cutaneous CD8+ T-cell pseudolymphoma [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
ecthyma gangrenosum [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
eruptive sebaceous hyperplasia [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
aspecific grade 3 skin reaction [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
Lupus miliaris disseminated faciei [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
palmo-plantar hyperkeratosis [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
pustules [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (5.9%)*	*0 (0%)*	*1 (3.3%)*
Therapy*						
n. patients [1]	n (%)	43 (15.4%)	0 (0%)	65 (52.4%)	1 (100%)	109 (26.9%)
systemic corticosteroids	n (%)	31 (72.1%)	0 (0%)	16 (24.6%)	0 (0%)	47 (43.1%)
topical corticosteroids	n (%)	5 (11.6%)	0 (0%)	38 (58.5%)	0 (0%)	43 (39.4%)
methotrexate	n (%)	0 (0%)	0 (0%)	6 (9.2%)	0 (0%)	6 (5.5%)
dupilumab	n (%)	1 (2.3%)	0 (0%)	1 (1.5%)	0 (0%)	2 (1.8%)
Others	n (%)	6 (14%)	0 (0%)	4 (6.2%)	1 (100%)	11 (10.1%)
IVIg [2]	*n (%)*	*3 (42.9%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*3 (15%)*
Dupilumab [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*2 (18.2%)*	*0 (0%)*	*2 (10%)*
Azathioprine [2]	*n (%)*	*1 (14.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (5%)*
Ceftazidime [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
Ciprofloxacin [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
Doxycycline [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
ECP [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
Fluconazole [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (50%)*	*1 (5%)*
Hydroxychloroquine [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
Ketoconazole [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (50%)*	*1 (5%)*
oral tacrolimus [2]	*n (%)*	*1 (14.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (5%)*
phototherapy [2]	*n (%)*	*1 (14.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (5%)*
Plasma exchange per TEN [2]	*n (%)*	*1 (14.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (5%)*
topical metronidazole [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
topical tretinoin [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
topical urea [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*
watch and wait [2]	*n (%)*	*0 (0%)*	*0 (0%)*	*1 (9.1%)*	*0 (0%)*	*1 (5%)*

*Note: For *Anatomical distribution* and *Therapy* variables, records considered NA if more than one patient was included in the study and more than one category was indicated without the distribution of patients within category.

[1] Percentage values are calculated by taking the total number of patients for each Lymphoma type as the denominator.

[2] Percentages values are calculated considering number of *Other* as denominator

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Figure 1: (A) (B)

Figure 2: PRISMA flowchart of the study. The selection process for study inclusion in the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.