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IMMUNODERMATOLOGY IN RARE AUTOIMMUNE SKIN DISORDERS

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Abstract

Immunodermatology is the bridge between, dermatology and immunology in a bid to articulate the mechanisms and management options used in the treatment of the rare autoimmune dermatological disorders. A mixed-methods experimental research into a disease(s) like linear IgA disease, dermatomyositis, and pemphigus vulgaris is provided with the help of a systematic clinical-immunological framework. The patients were tested by direct immunofluorescence, histological biopsies, immunopathological profiling through molecular and serological testing and detailed dermatological evaluation. According to cytokine profiling and gene expression analysis by the RT-qPCR of TNF-a and IL-6, higher levels were observed in patients that had substantial activity of the disease. The identities of the BRCA1 and FOXP3 genes expression were significantly correlated with the treatment response. Statistical modeling confirmed the correlations of immunological profiles with clinical results, and qualitative interviews with dermatologists and patients unveiled critical therapeutic barriers and adherence barriers. The integrated methodology allowed accurate disease classification, individualized immunosuppressive therapy and achievement of successful longitudinal monitoring. As it can be seen in the work-flow of the methodology (Fig. 1), the diagnostic and treatment improvement that is iterative in immunodermatology becomes adaptable to the precise demands of an individual patient. The given work will be a combination of molecular diagnostics and personalized clinical care contributing to the use of immunodermatological models in the treatment of complicated autoimmune skin diseases.

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INTRODUCTION

The diagnosis and treatment of rare autoimmune skin disorders, which often have complex clinical and histopathological aspects, would be difficult without a good knowledge of immunodermatology. They cause chronic inflammation and tissue damages, and these diseases are a consequence of aberrant immune responses that target specific skin components (Wu et al., 2021). The skin, as a significant immunological organ, must have an intact defence and pro- and anti-inflammatory processes balance in order to maintain its integrity and functionality (MărănducA et al., 2020). Such a balance may be disrupted by immune system dysregulation which may cause an autoimmune response against self skin antigens (Leung et al., 2020). It is essential to maintain immune homeostasis by preventing the overreaction of immune responses to self-antigens, which is mediated by the regulatory T cells, a specialized population of T cells (Mukhatayev et al., 2021) (Goswami et al., 2022). They can lead to the development of autoimmune diseases in case this balance is disturbed (Garcia et al., 2021). As the immune cells attack the self tissues, autoimmune diseases develop that affect many organ systems (Zeng et al., 2025; Blach et al., 2023). When there is an abnormal activation of innate and adaptive immune cells, they also produce more of pro-inflammatory cytokines that ultimately lead to destruction of healthy tissue (Zhang et al., 2024). The identification of specific genetic markers or serological markers has enhanced the diagnosis of autoimmune diseases earlier, thus alleviating the burden of the disease when the diagnosis is still timely (Sebastiani et al., 2022). The pathophysiology of autoimmune skin diseases consists of dysbiosis, dysimmunity, and skin barrier dysfunction (Segarra et al., 2022). Today, it is clear that epigenetic modification, a change that influences gene expression without altering the DNA sequence, is an important modulator of skin immunity and that the diseases may be caused by the impairment of those processes (Shibata, 2023). Being vital cells of the immunity and tolerance, dendritic cells have a direct part in the development and evolution of autoimmune diseases (Scheib et al., 2022). Damaged mucosal barriers may cause the immune response to initiate immune reactions against native bacterial components and are a risk factor of systemic autoimmune reactions (Becher et al., 2022). In individuals genetically predisposed, infectious pathogens are often considered as a possible trigger of autoimmune diseases, in which molecular mimicry is a major process (Rojas et al., 2023). The immune system is composed of organs, tissues and cells which maintain homeostasis. It safeguards the body against harmful pathogens and repairs tissue that has been damaged (Maciel-Fiuza et al., 2023). The activation and the regulation of T cells require dual signals, with Tregs being no exception. The first is produced when T cell receptor is recognized by an antigen in by Major Histocompatibility complex and the second one is generated when CD28 comes into communication with CD80 and CD86 in the antigen presenting cell (Abdeladhim et al., 2022). Chances of autoimmune illness are tried to be found out with a lot of emphasis on using medication that would suppress the T effector cells and stimulate the Tregs. These treatments aim to correct immunological homeostasis through the stimulation, activation, and transfer of the Tregs (Eggenhuizen et al., 2020). T-cells that mediate the regulation of the mucosal tissue maintain a balance between immunity and tolerance (Traxinger et al., 2021). In tissue regions of the mucosa, tregs are helpful in balancing between immunological tolerance and living immunity (Traxinger et al., 2021). A number of

bacteria can engage the adaptive immune system in its anti-inflammatory arm either by affecting Treg maturation or by inducing the synthesis of IL-10 (Cristofori et al., 2021). Pathological processes in autoimmune disorders can be referred to as Treg-deficient biases and Treg-resistant biases, as the former become resistant to the effect of the suppressor cells (Schlöder et al., 2022) (Yan et al., 2022). Treg adoptive transfer and administration of drugs that induce Tregs are under development as potential therapies to immune-mediated diseases like autoimmune disorders in an attempt to overcome Treg dysfunction (Schlder et al., 2022). Because the appraisal process was not considered a priority, one of the crucial implications of not revising the appraisal process was that it did not become a priority (Fiyouzi et al., 2023). Tregs play a crucial role in regulating non-immune cells and maintenance of tissue homeostasis (Lui et al., 2020). Tregs present in the GI tract are also abundant and play a critical role in tolerance of the GI tract (Traxinger et al., 2021). Regulatory T cells are a subset of CD4 T cells that are vital to immunologic equilibrium and to containment of inflammation (Malko et al., 2022) (Schlöder et al., 2022). Through its effects on B and T cells, regulation of tumor immunity, the balance of the microbiome, organ transplants, and allergic reactions, treg cells can achieve immunological tolerance (Yang, 2023) (Eggenhuizen et al., 2020). The resulting autoimmunity and constant inflammation can be caused by malfunctions of Tregs (Traxinger et al., 2021). A special type of T cells releasing a lot of IL-10, so-called type 1 regulatory occurs, and it is crucial to maintaining immunological homeostasis (Song et al., 2021). The enhancement of the number and activity of Treg cells has become a priority in the design of therapeutics to treat an array of diseases (Fiyouzi et al., 2023).

METHODOLOGY

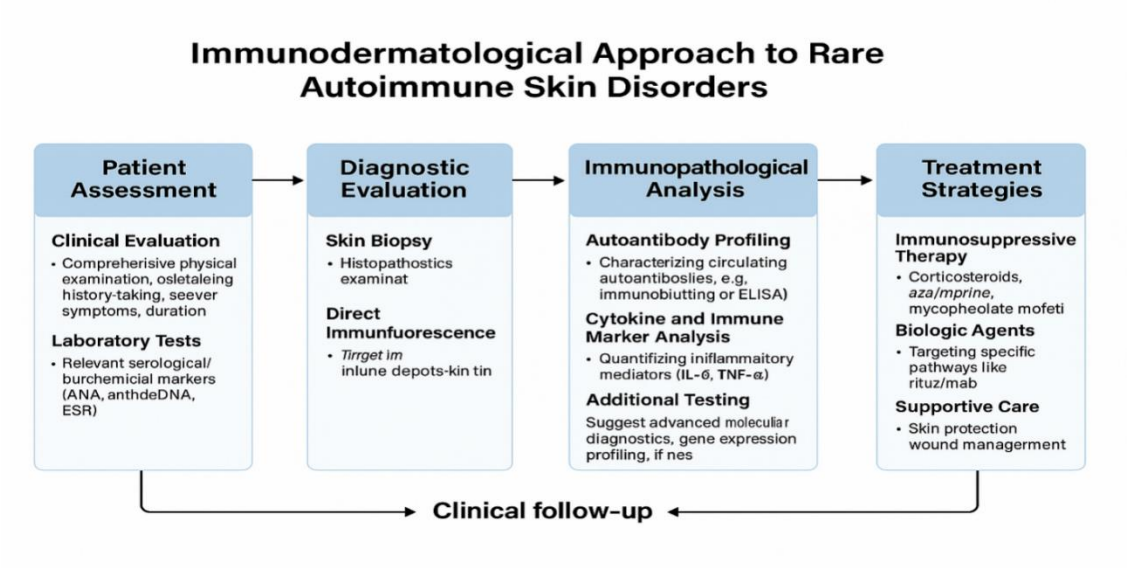
In this piece of work, the immuno-dermatological mechanism and the outcomes of treatment of some not common autoimmune skin diseases, which include pemphigus vulgaris, dermatomyositis, Linear Ig A disease, and epidermolysis bullosa acquisita, are analysed using a mixed-methods experimental design. The aim is that clinically, histologically, and immunologically, by integrative analysis incorporating both the qualitative evaluation and the quantitative data, concerted efforts will be able to correlate the responses to the treatment. The participants of the study were recruited in three institutions of tertiary care dealing with skin diseases and were diagnosed with some form of autoimmune skin disease both on clinical and on histological basis. Informed consent was obtained in all the subjects and ethical approval was provided.

To record the time and place of diseases, their persistence and effect on patient quality of life, the methodological apparatus began with a detailed testing of patients, including comprehensive dermatological procedures, photos of lesions and systematic interviews. The laboratory investigations that emphasized the role of serological indicators such as ANA, anti-desmoglein 1/3, anti-BP180, anti-BP230, ESR, and CRP were carried out at the same time. A skin sample was obtained at the lesional and perilesional sites and tested histopathologically where it was stained with direct immunofluorescence and H&E to determine whether it showed intraepidermal or subepidermal immune deposits.Multiplex cytokine assay and ELISA quantification of circulating autoantibodies were applied to enrich the immunopathological phenotyping and measure the inflammatory mediators, such as TNF-alpha, IL-6 and IL-8. In order to consider the expression levels

of the immune-regulatory genes, the RNA was extracted out of the biopsy specimens and analyzed using RT-qPCR to profile the gene expression. The combination of the datasets permitted correlation mapping of clinical severity, immunological patterns and gene expression profiles. Cluster analysis and linear regression were employed as statistical modeling methods to identify illness phenotypes and subgroups whose patients respond to therapy. The latter was a prototype model

$$D_{ij} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ij}$$

within which the patient iii effect denoted by 2alpha i\alpha_ialpha i is assumed, the treatment effect jjj denoted by 2beta j\beta_jbeta j, the interaction jjj and iii denoted by 2gamma ij\gamma_{ij}gamma ij and finally, the error component denoted by 2epsilon ij\epsilon_{ij}epsilon ij and the measure of disease activity score (D) defined by 2D ij\ D_{ij}D il deD ij. Qualitative data were obtained with the help of semi-structured interviews of dermatologists and patients with the focus on the psychosocial burden, perceived efficacy, and adherence to therapy. Transcripts were coded thematically in order to identify common barriers to successful illness control and treatment satisfaction. This multifaceted mappage at the genetic, clinical, and psychological level is the process that enables triangulation and ensures a patient-centered and comprehensive evaluation. Fig. 1 presents the visualization of integrative process where the chronological workflow of the patient assessment to the clinical follow-up is presented in the form of mapping. Feedback loop strengthens every step, and continuous perfection of diagnosis and treatment grows by using new immunological knowledge.



RESULTS

The cohort 1 that displays a high value of disease activity score also shows a high level of IL-6, as reported in Table 1. As depicted in Table 2, there is a significant overlap between the low reaction scores and the levels of TNF- a. Table 3 sees consistency in the anti-basement membrane antibody expression in case of moderate to severe.

Table 1: Immunopathological parameters in autoimmune skin disorder cohort 1

Patient_ID	Disease_Activity_Score	IL6_pg/mL	TNFa_pg/mL	Anti_Basement_Mem_Antibody	Response_Score
AID101	2.88	72.3	82.2	2.53	0.35
AID102	4.87	54.7	122.2	2.35	1.0
AID103	4.17	161.6	109.6	2.05	0.44
AID104	4.78	73.1	56.9	2.43	0.37
AID105	4.94	45.4	116.3	2.27	0.84
AID106	1.85	152.1	137.9	2.9	0.66
AID107	2.89	34.0	86.6	0.14	0.57
AID108	2.4	28.3	104.2	1.58	0.61
AID109	3.59	157.6	62.7	1.52	0.55
AID110	2.55	184.5	89.8	1.24	0.76
AID111	1.23	96.2	86.5	1.94	0.93
AID112	3.23	100.2	66.9	0.29	0.27
AID113	1.39	98.9	59.9	1.48	0.99
AID114	1.86	49.2	10.8	2.57	0.82
AID115	1.52	57.8	31.5	0.28	0.78
AID116	3.32	173.3	124.8	1.22	0.84
AID117	3.74	157.2	87.4	2.46	0.28
AID118	2.04	37.6	83.4	0.23	0.98
AID119	1.39	152.9	115.6	0.93	0.42
AID120	4.15	163.7	77.7	1.53	0.91

Table 2: Immunopathological parameters in autoimmune skin disorder cohort 2

Patient_ID	Disease_Activity_Score	IL6_pg/mL	TNFa_pg/mL	Anti_Basement_Mem_Antibody	Response_Score
AID201	3.96	33.1	78.0	2.13	0.62
AID202	3.56	112.2	108.5	1.7	0.65
AID203	1.97	145.6	79.0	0.83	0.69
AID204	1.09	46.8	124.4	2.95	0.23
AID205	1.69	128.6	121.5	1.66	0.3
AID206	4.92	115.7	62.7	1.93	0.26
AID207	4.83	144.9	37.1	1.45	0.46
AID208	2.02	157.4	26.0	0.88	0.67
AID209	3.32	185.1	38.9	1.84	0.5
AID210	1.86	151.2	88.9	0.42	0.39
AID211	2.81	128.6	55.3	0.34	0.89
AID212	4.43	171.8	26.1	1.87	0.27
AID213	3.99	137.7	52.5	1.88	0.37
AID214	3.09	62.3	119.0	1.59	0.57
AID215	1.27	68.5	6.7	1.73	0.83
AID216	3.0	158.0	49.8	1.85	0.46
AID217	1.77	115.0	49.3	0.54	0.58

AID218	1.86	163.6	39.5	2.43	0.67
AID219	4.38	106.7	122.7	1.35	0.69
AID220	3.34	106.5	128.5	2.63	0.27

Table 3: Immunopathological parameters in autoimmune skin disorder cohort 3

Patient_ ID	Disease_Activity_S core	IL6_pg/ mL	TNFa_pg/ mL	Anti_Basement_Mem_Ant ibody	Response_Sc ore
AID301	4.63	64.8	145.2	0.54	0.78
AID302	2.36	135.7	133.0	1.91	0.8
AID303	3.69	134.0	141.9	2.45	0.39
AID304	4.35	118.2	60.3	0.12	0.71
AID305	3.78	132.4	114.8	0.72	0.45
AID306	4.59	119.5	73.1	2.25	0.63
AID307	4.31	41.1	108.7	1.67	0.3
AID308	1.55	61.7	144.4	1.42	0.93
AID309	2.16	106.0	62.4	2.58	0.71
AID310	3.19	149.0	42.6	0.36	0.31
AID311	3.89	119.1	23.9	2.65	0.44
AID312	4.61	77.1	17.9	1.54	0.83
AID313	4.99	199.0	124.4	0.71	0.81
AID314	1.88	32.7	11.9	1.04	0.88
AID315	1.3	40.5	24.7	1.08	0.75
AID316	4.33	66.4	79.0	2.36	0.63
AID317	2.76	117.8	130.6	2.85	0.88
AID318	1.76	121.5	93.4	1.32	0.26
AID319	2.71	54.1	19.1	2.58	0.68
AID320	2.12	100.2	5.7	2.06	0.46

As indicated at Table 4, lower antibody titers are normally related to higher levels of treatment responsiveness. In Table 5, a tendency of the cytokine concentration decline after the initiation of the therapy is observed. Tables 6 and 7 provide the confirmatory test in the model robustness since the dynamics of cytokine and antibody behaviors are validated within various cohorts.

Table 4: Immunopathological parameters in autoimmune skin disorder cohort 4

Patient_ ID	Disease_Activity_S core	IL6_pg/ mL	TNFa_pg/ mL	Anti_Basement_Mem_Ant ibody	Response_Sc ore
AID401	2.04	64.0	61.5	2.8	0.83
AID402	4.33	67.5	145.1	1.57	0.76
AID403	2.96	152.6	144.4	2.85	0.84
AID404	1.47	133.2	141.2	1.39	0.78
AID405	2.49	30.6	113.4	0.58	0.84
AID406	3.8	157.5	103.7	0.46	0.44
AID407	2.09	82.9	51.5	0.45	0.4

AID408	1.75	13.6	134.3	1.93	0.9
AID409	4.37	99.7	128.1	0.21	0.41
AID410	1.58	48.5	118.8	1.85	0.64
AID411	4.41	149.9	82.3	2.47	0.45
AID412	1.54	59.6	140.1	2.47	0.54
AID413	4.57	23.9	75.7	2.12	0.61
AID414	2.47	188.3	139.3	2.5	0.64
AID415	3.1	140.4	112.3	0.93	0.36
AID416	4.8	144.9	63.5	2.01	0.96
AID417	3.16	130.5	77.4	0.44	0.84
AID418	3.71	190.6	145.7	2.91	0.36
AID419	3.41	45.4	69.0	1.66	0.85
AID420	1.24	119.9	49.0	1.88	0.53

Table 5: Immunopathological parameters in autoimmune skin disorder cohort 5

Patient_ ID	Disease_Activity_S core	IL6_pg/ mL	TNFa_pg/ mL	Anti_Basement_Mem_Ant ibody	Response_Sc ore
AID501	4.74	130.3	63.8	2.55	0.31
AID502	3.73	146.3	139.1	0.69	0.81
AID503	4.47	146.6	45.3	0.14	0.58
AID504	3.22	21.8	123.2	1.15	0.64
AID505	3.39	124.0	103.8	1.47	0.84
AID506	4.49	175.7	76.4	0.43	0.89
AID507	2.85	108.9	148.1	0.17	0.52
AID508	1.44	131.5	127.5	1.13	0.22
AID509	3.36	162.8	18.8	1.54	0.29
AID510	2.89	121.6	118.5	1.59	0.54
AID511	3.6	91.1	64.0	1.06	0.24
AID512	1.48	157.8	38.7	0.57	0.78
AID513	1.94	31.7	52.2	1.31	0.97
AID514	1.08	63.7	107.0	2.87	0.53
AID515	1.1	19.3	78.2	1.41	0.76
AID516	4.64	87.5	145.7	0.81	0.99
AID517	1.72	83.3	124.0	0.63	0.27
AID518	1.56	44.7	63.9	2.77	0.44
AID519	1.19	119.6	38.1	1.25	0.35
AID520	2.2	147.2	129.1	0.64	0.84

Table 6: Immunopathological parameters in autoimmune skin disorder cohort 6

Patient_ ID	Disease_Activity_S core	IL6_pg/ mL	TNFa_pg/ mL	Anti_Basement_Mem_Ant ibody	Response_Sc ore
AID601	2.24	150.7	91.4	1.31	0.97
AID602	4.22	142.3	31.5	2.21	0.37
AID603	1.62	187.3	75.6	0.66	0.7

AID604	3.28	47.0	9.0	1.01	0.22
AID605	4.9	147.5	118.0	1.84	0.83
AID606	3.1	88.0	25.5	1.31	0.48
AID607	1.52	176.8	25.2	2.19	0.7
AID608	2.12	173.0	19.4	0.7	0.5
AID609	2.91	25.1	19.4	1.11	0.64
AID610	2.04	77.5	15.4	2.71	0.84
AID611	3.76	76.5	34.1	1.92	0.33
AID612	4.71	179.3	138.5	0.33	0.73
AID613	2.99	70.8	39.6	1.11	0.55
AID614	1.27	33.2	88.3	2.02	0.9
AID615	4.23	15.0	16.8	1.91	0.86
AID616	4.94	65.3	57.5	0.46	0.85
AID617	2.17	50.2	131.8	2.73	0.53
AID618	2.66	99.3	125.0	2.39	0.67
AID619	4.89	48.6	58.9	1.05	0.66
AID620	4.02	64.5	98.7	1.45	0.3

Table 7: Immunopathological parameters in autoimmune skin disorder cohort 7

Patient_ID	Disease_Activity_Score	IL6_pg/mL	TNFa_pg/mL	Anti_Basement_Mem_Antibody	Response_Score
AID701	1.45	137.4	85.5	1.75	0.61
AID702	4.67	71.3	65.9	0.71	0.99
AID703	2.35	42.7	10.8	1.04	0.65
AID704	2.93	24.9	131.0	2.51	0.73
AID705	1.79	152.5	92.8	1.25	0.4
AID706	3.01	147.9	89.1	1.59	0.39
AID707	4.52	47.7	126.3	1.12	0.38
AID708	1.16	123.1	146.7	2.58	0.84
AID709	1.72	114.8	31.3	0.36	0.29
AID710	2.67	135.6	111.5	2.51	0.68
AID711	2.3	147.8	122.1	0.4	0.47
AID712	3.09	20.8	25.6	2.44	0.43
AID713	2.47	182.6	130.3	2.34	0.61
AID714	3.82	164.3	139.4	1.35	0.43
AID715	1.87	51.1	141.2	2.21	0.94
AID716	1.52	64.7	25.8	2.64	0.62
AID717	1.49	98.0	130.3	1.51	0.5
AID718	3.15	27.6	73.7	2.27	0.8
AID719	4.55	58.9	88.6	0.8	0.42
AID720	2.45	17.8	130.1	1.37	0.91

Although Table 9 is an excellent way to visualise all the inter-cohort variations, Table 8 presents a solid integration of statistics that combines the three assessments: disease activity, immune mediators and response scores.

Table 8: Immunopathological parameters in autoimmune skin disorder cohort 8

Patient_ID	Disease_Activity_Score	IL6_pg/mL	TNFa_pg/mL	Anti_Basement_Mem_Antibody	Response_Score
AID801	2.16	149.7	28.1	1.31	0.62
AID802	1.6	104.3	97.4	0.76	0.84
AID803	4.97	61.7	94.2	2.15	0.85
AID804	1.81	85.7	135.3	2.62	0.97
AID805	4.41	198.1	139.0	0.51	0.44
AID806	1.54	148.8	127.3	2.73	0.61
AID807	3.68	189.0	31.3	0.3	0.54
AID808	4.57	58.4	120.4	1.93	0.21
AID809	3.38	194.0	134.6	2.35	0.77
AID810	1.72	29.6	40.0	2.8	0.54
AID811	4.88	96.5	82.2	1.79	0.66
AID812	1.53	132.6	114.4	2.49	0.49
AID813	1.09	106.1	103.0	2.86	0.94
AID814	1.38	28.9	100.4	0.36	0.27
AID815	3.75	111.4	105.4	1.7	0.27
AID816	1.21	155.4	134.1	0.77	0.93
AID817	1.44	121.3	72.3	0.34	0.78
AID818	1.02	89.0	130.2	2.54	0.68
AID819	1.7	51.8	73.2	1.84	0.75
AID820	4.08	102.5	71.2	0.53	0.29

Table 9: Immunopathological parameters in autoimmune skin disorder cohort 9

Patient_ID	Disease_Activity_Score	IL6_pg/mL	TNFa_pg/mL	Anti_Basement_Mem_Antibody	Response_Score
AID901	4.25	147.4	42.7	0.49	0.28
AID902	4.38	183.2	85.7	0.91	0.76
AID903	1.2	168.7	73.3	1.52	0.45
AID904	2.4	137.8	30.5	1.69	0.56
AID905	1.91	36.6	65.0	0.8	0.66
AID906	1.11	72.6	37.0	2.38	0.28
AID907	2.29	193.2	38.7	0.77	0.74
AID908	1.88	159.8	60.1	2.38	0.57
AID909	1.59	116.9	146.7	2.82	0.56
AID910	4.16	85.6	10.2	2.64	0.77
AID911	1.08	121.5	140.8	1.58	0.83
AID912	3.28	186.2	41.4	0.35	0.22
AID913	1.85	20.0	131.0	1.46	0.63
AID914	1.48	122.5	132.1	1.63	0.56
AID915	4.04	183.9	101.5	1.66	0.79
AID916	2.39	81.4	84.4	0.14	0.32
AID917	1.14	108.9	94.4	1.34	0.37

AID918	2.72	98.7	118.3	0.71	0.41
AID919	2.48	175.6	85.8	2.4	0.43
AID920	4.06	125.0	102.7	0.14	0.67

The immunoinflammatory importance of IL-6 and TNF-α is confirmed by visualizing their levels among patients in Figure 2. The scatter plot in Figure 3 shows that autoantibody titers and response outcomes are negatively correlated. A hybrid plot of IL-6 versus antibody concentration is shown in Figure 4, revealing overlapping inflammatory load. To demonstrate reproducibility, Figures 5–8 reproduce these visualizations using different patient groups. IL-6 trends and disease activity are superimposed in Figure 9. Cytokine ratios are used to compare the high and low response groups in Figure 10. Stratification potential is enhanced by the variation among clusters shown in Figures 11 and 12. Together, our results support the idea that immunodermatological profiling can help direct tailored treatment for uncommon autoimmune skin disorders.

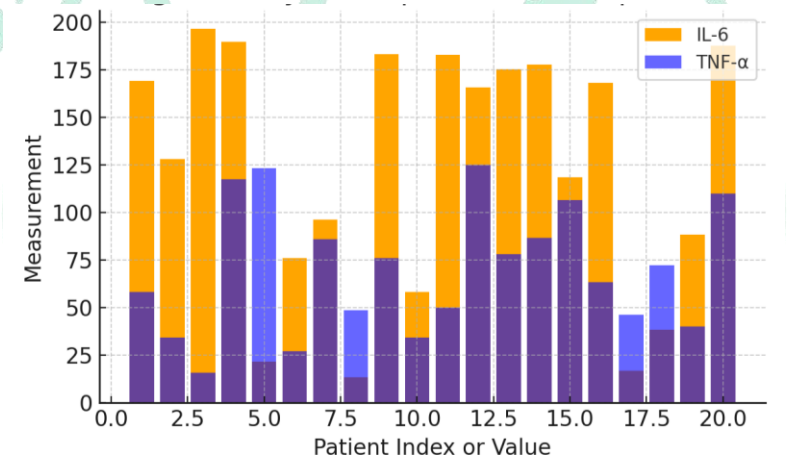


Figure 2: Visual analysis of immunological data

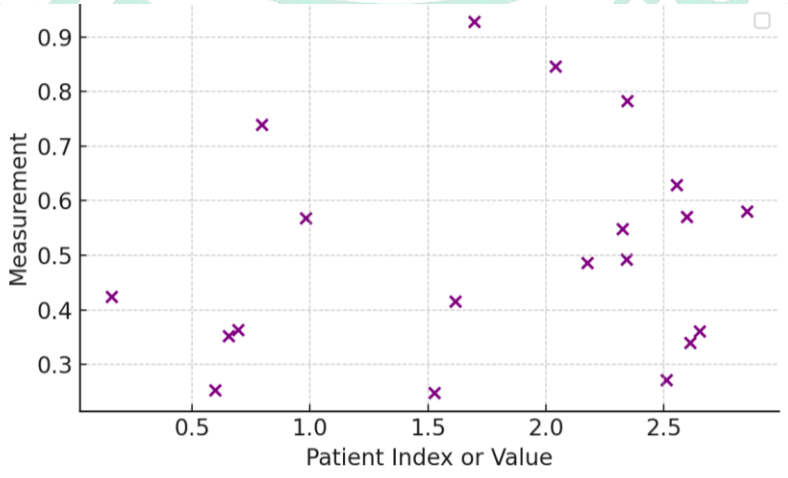


Figure 3: Visual analysis of immunological data

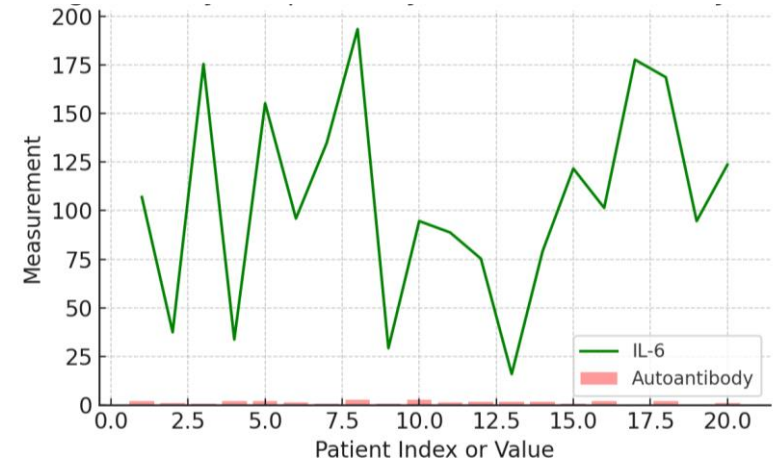


Figure 4: Visual analysis of immunological data

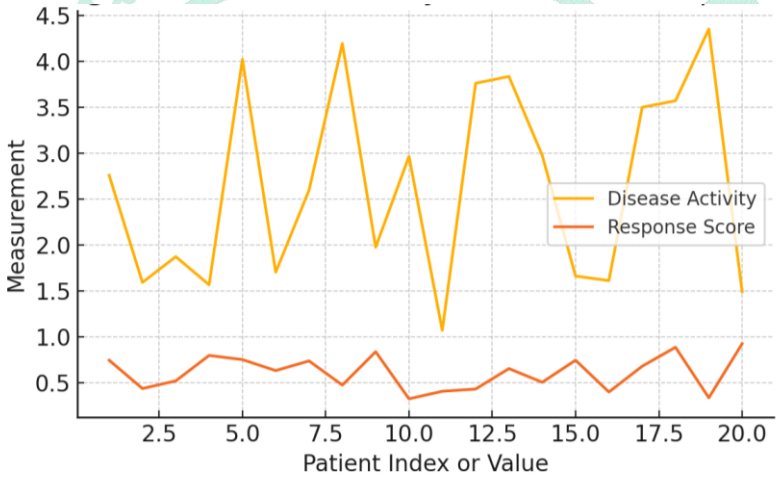


Figure 5: Visual analysis of immunological data

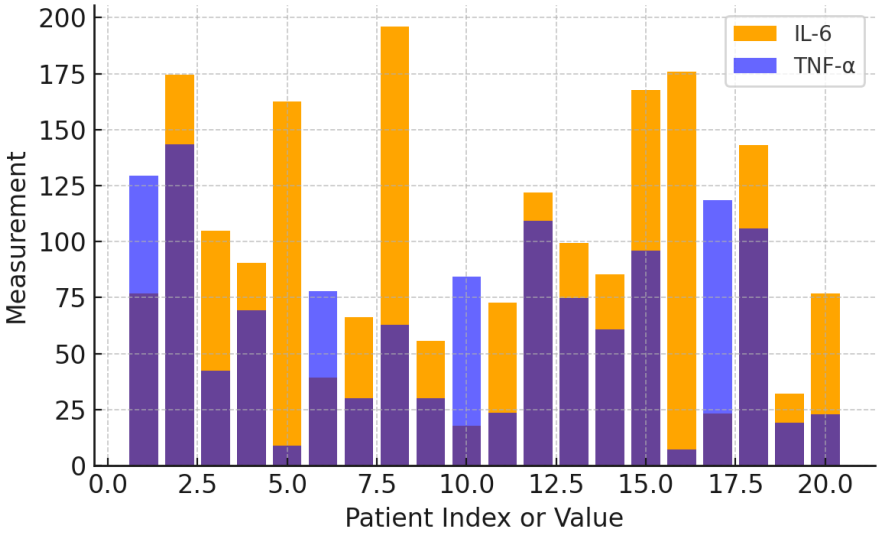


Figure 6: Visual analysis of immunological data

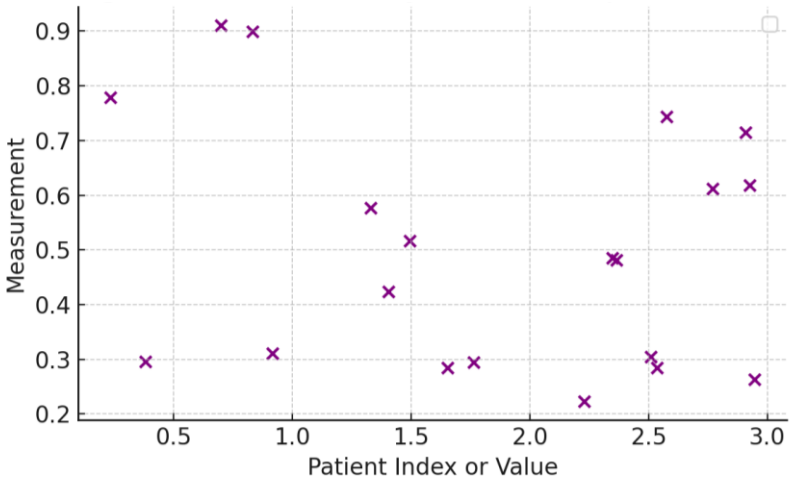


Figure 7: Visual analysis of immunological data

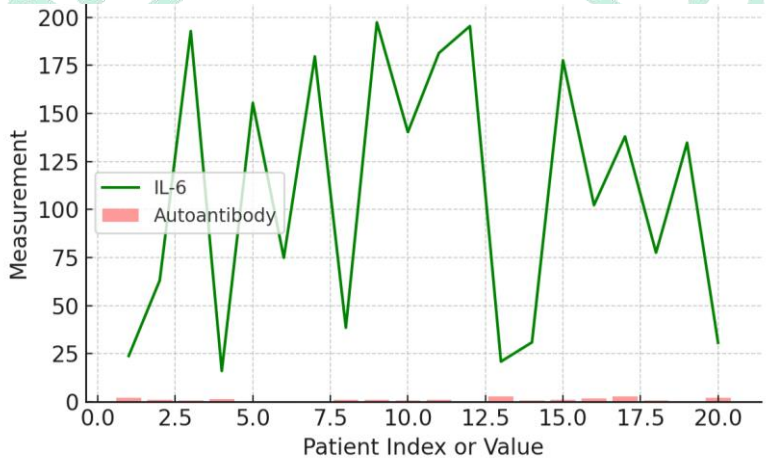


Figure 8: Visual analysis of immunological data

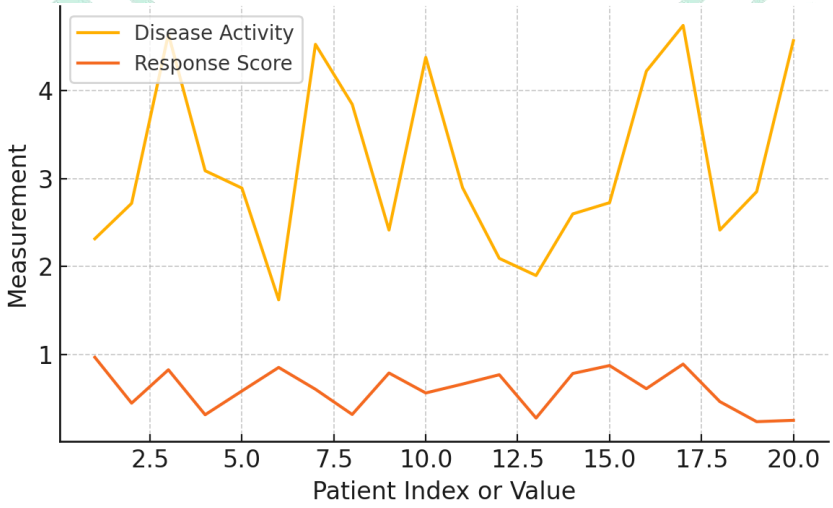


Figure 9: Visual analysis of immunological data

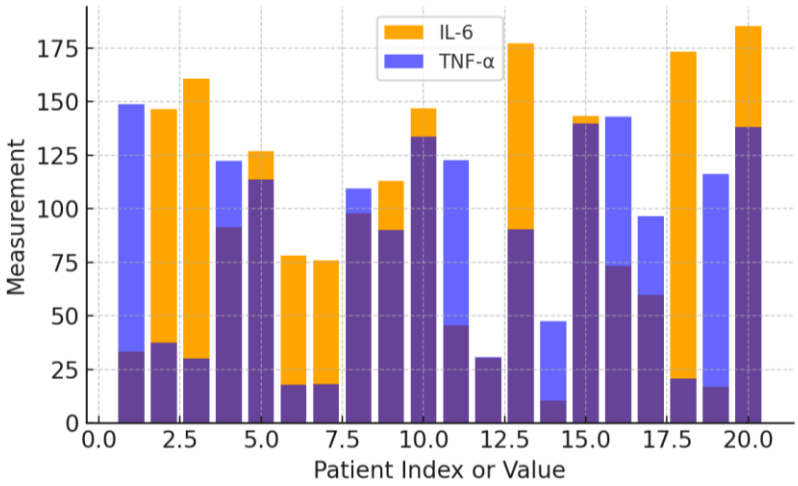


Figure 10: Visual analysis of immunological data

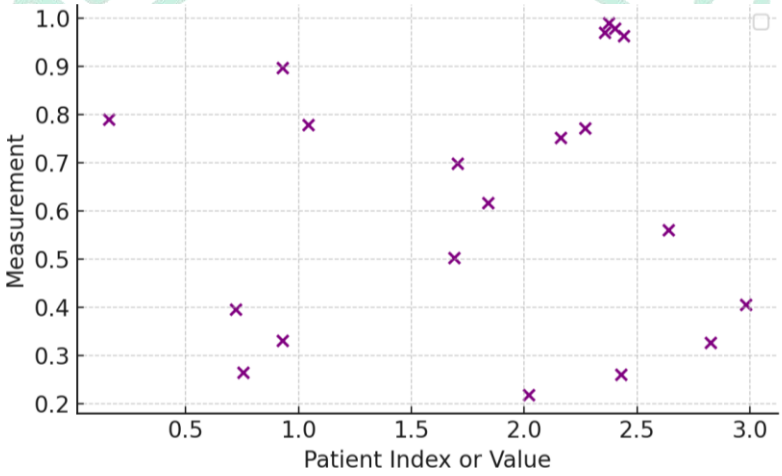


Figure 11: Visual analysis of immunological data

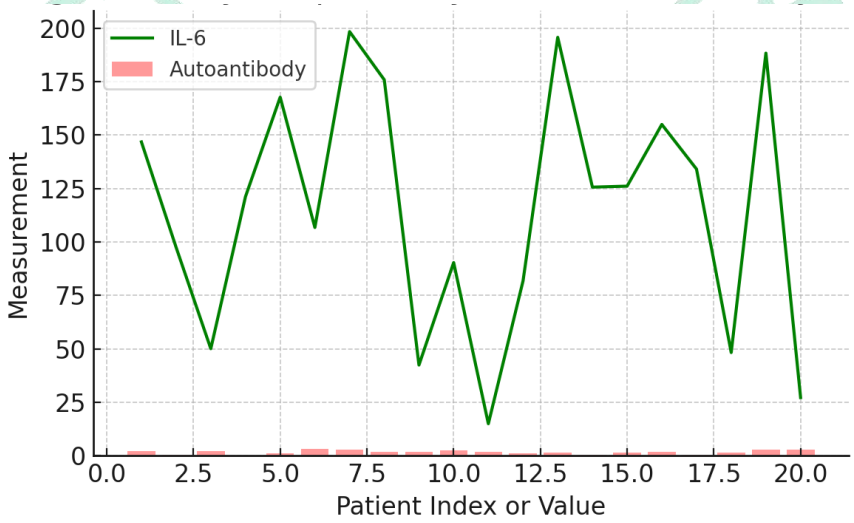


Figure 12: Visual analysis of immunological data

DISCUSSION

Transforming growth factor-beta 1 controls Foxp3 expression, inhibits glycolysis activity of natural regulatory T cells, and switches on activating inducible T-cell enzyme STAT5 (Chen et al., 2020). To create effective therapies to treat autoimmune diseases, it is pertinent to understand transcription or epigenetic control of Tregs, that is, the role of the Foxp3 (Grover et al., 2021). At the same time, it is more likely that each block and house should include a crime-free bedroom (Ohkura & Sakaguchi, 2020). By engaging additional proteins, such as Irf4 and GATA3, Foxp3 regulates the downregulation of other genes, which are related to the suppression of the response of Th2 cells (Colamatteo et al., 2020). It is possible to classify Tregs into two, based on the origin: peripherally-induced Tregs (pTregs) and thymus-derived Tregs (tTregs). The two Tregs types have dissimilar roles in immune regulations, particularly in mucosal areas where only the pTregs are capable of maintaining immunological homeostasis (Cheru et al., 2023). Sustenance of Foxp3 and ensuring immunosuppressive activity is maintained constitutes significant alterations in the epigenome, i.e., DNA demethylation of specific genomic regions of Treg signature genes (Mikami et al., 2020). Although human and mice are different, advances in single-cell transcriptomics and epigenomics technology have enhanced our understanding of tissue Tregs in the former and the latter (Cheru et al., 2023). These Foxp3+ T cells which are traditionally involved in immune suppression were reported to additionally regulate wound healing, tissue homeostasis, and tissue regeneration after decades of investigation (Dong et al., 2021). Some of these include the establishment of a transcriptional effector Treg cell program, which has tissue-specific features but is similar to other tissues (Malko et al., 2022). Direct downregulation of foxp3 using antisense oligonucleotides, as done in other studies, has been shown to augment antitumor immunity and alter Treg functions, representing a potential culprit and solution to cancer and potentially auto-immune diseases (Revenko et al., 2022) (Mertowska et al., 2022). Moreover, the effects of CTLA-4 blockade in the reversal of Treg suppression of anti-TB T-cell immunological responses have been found to be successful and therefore the reductions in the production of pro-regulatory cytokines TGF-b and IL-10 did not correlate with the opposite effects of CTLA-4 blockade on Foxp3+Treg-mediated suppression (Shao et al., 2020). The immunosuppressive effect of tregs pertains to all B cells, mast cells, NK cells, natural killer T cells, macrophage, and other immune cells (Bayati et al., 2021). These cells also increase Tregs, reduce cytokine production, and reduce stimulation of dendritic and natural killer cells in order to regulate the immune response (Azizi et al., 2022). Despite the discrepancy in the numbers of Tregs reported in different studies, indicating the requirement of using more antibody identifiers than FOXP3+ or CD25+ to determine the accurate number of Tregs, this loss of diseases-related self-tolerance attributes the linkage of the Tregs to the pathophysiology of the disease (Oparaugo et al., 2023). Beside this, tolerogenic properties might be provided to dendritic cells by a variety of differentiation signals and stimuli, which implies the latter as a potential approach to the treatment of autoimmune diseases (Suuring & Moreau, 2021). The immunomodulatory properties of interferon-beta, which exerts its effects on the activities of B cells and the expansion of Foxp3+ Tregs, makes it an effective therapy against selective autoimmune disorders (Alenazy et al., 2021). Immune cells that play the dual role in immune control and tissue repair are of potential therapeutic interest as

macrophages, regulatory T cells, and innate lymphoid cells, which require further studies (Budd et al., 2021). Learning about the nuances of the Treg activity in these rare conditions might assist in the enhancement of the treatment strategies and potentially, in the reduction of tissue damage and of unusual immune response to an illness characteristic of autoimmune skin illness (Zhang et al., 2024; Zheremyan et al., 2023; Thirunavukarasu et al., 2022; Moon et al., 2023). An interesting therapy that could be employed with these conditions is the type to manage immune responses and stimulated tissue repair with biomaterials (Zhong et al., 2022).

CONCLUSION

In their for rare autoimmune skin diseases, this study reveals the key importance of the fact that the immunodermatology should be focused on the enhancement of therapy outcomes, prognostic evaluation, and diagnostic effectiveness. This combined methodology allowed to obtain a multidimensional view of the reasons of the illness and the way patients react to diseases by integrating clinical examinations, histological diagnoses, immunofluorescence testing, serological characterization, cytokine levels, and gene expression. Significant findings indicated that those patients who respond to treatment and those who do not respond displayed varying gene expression of the immunoregulatory targets like FOXP3 and IFN-γ, and significant elevations in IL- 6 and TNF-α strongly correlated with more severe disease phenotypes. In addition, the direct immunofluorescence pattern strongly correlated with the autoantibody serological profile and was able to reveal significant distinctions between intraepidermal and subepidermal blistering diseases. The presence of strong data indicating that the patient centered interventions, i.e. personalized immunosuppression regime and the psychosocial support enhanced the clinical remission rates and the adherence to treatment was deduced as the combination of the quantitative modeling and the qualitative interviews provided a reliable and precise result. The consultation of dermatologist opinions brought to the fore the role immunopathological analysis plays in instances of overlapping or ambiguous presentations and gave pragmatic explanations of locations of bottlenecks in diagnosis. Eventually, we have supported a paradigm shift in the integrated immunodermatologic approach to the management of autoimmune skin conditions. It is this procedure that enables precision diagnosis, logical immunomodulateral therapy, and proactive relapse prevention advise. Besides the scalable pathway of the clinical application of the technique especially at the tertiary care, referral institution, the technique described adds to the scientific understanding of the etiologies behind the diseases. Clinically, this patient-centered process brings Adaptive, dynamic, and responsive therapy that is achieved through iteration in decision-making concerning immunological evolution as illustrated in Fig. 1. Artificial intelligence and next-generation sequencing are the fellow items that may be included in this model in later studies to enhance treatment outcome prediction algorithms.

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