Persistent Inadequate Disease Control and Therapeutic Inertia in Moderate-to-Severe Atopic Dermatitis: A 12-month Longitudinal Analysis of Real-world Outcomes from the TARGET-DERM AD registry

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Introduction

- Therapeutic inertia is the delay or reluctance in modifying treatment despite treatment goals not being met.
- According to the AHEAD treat-to-target recommendation1, if the agreed treatment targets are not achieved within 3 to 6 months, the treatment response is considered inadequate, and a modification of therapy should be considered.
- Therapeutic inertia is a significant challenge in managing atopic dermatitis (AD) and can lead to suboptimal control of the disease, affecting patient outcomes.
- The extent of therapeutic inertia in AD patients receiving systemic treatment in real-world clinical practice may be underestimated.

Objective

- To evaluate the occurrence of therapeutic inertia (assessed as non-escalation of therapy despite inadequate disease control) and the proportion of patients with moderate-to-severe AD who continue to show an inadequate response after receiving systemic therapies for a duration of 3 to 12 months.

Methods

- We evaluated both clinician- and patient-reported outcomes to determine the proportion of patients who did not meet moderate or optimal treatment targets, as defined by the AHEAD guidelines (Table 1).
- AD patients treated with their first advanced systemic therapy (AST), including abrocitinib, dupilumab, tralokinumab, and upadacitinib, or conventional systemic therapy (CST) including methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, systemic corticosteroids, and phototherapy were identified.
- Inclusion Criteria
  - Enrolled in TARGET-DERM AD, an observational, longitudinal study of participants with AD across 39 academic and community centers in the United States and Canada
  - All ages included
  - Patient treated with first systemic therapy either advanced or conventional
  - Patient had a validated Investigators Global Assessment of AD (vIGA-AD) score of 3 or 4 within 45 days prior to systemic initiation or up to 14 days after
  - Patient had at least one vIGA-AD assessment 3-12 months after systemic therapy initiation
- Exclusion criteria
  - Patient had received advanced or conventional systemic AD therapy prior to index date

Figure 1. Study Schematic

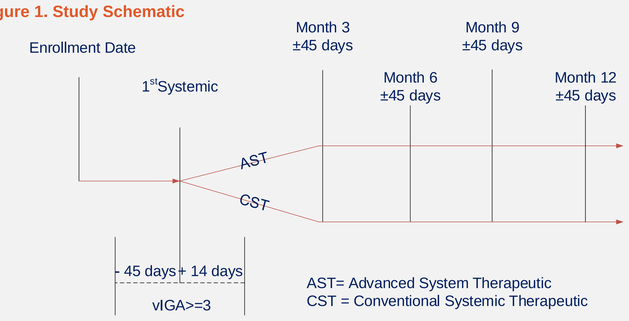

Table 1. Outcome Targets

Outcome	Moderate Target	Optimal Target
Skin Clearance	IGA ≤2 and 50% BSA improvement	IGA 0/1 and BSA ≤2%
Itch relief	WI-NRS ≥4-point improvement (reduction)	WI-NRS 0/1

- Assessments
  - The Investigators Global Assessment of AD (IGA, range 0–4)
  - Body surface area (BSA, range 0-100%) affected by AD
  - Patient-Reported Outcome Measurement Information System (PROMIS) Itch-Severity question evaluating Worst-Itch, (range 0–10)
- Analyses
  - Patient characteristics were summarized using descriptive statistics
  - The frequency and proportion of patients not achieving moderate or optimal outcome targets at 3, 6, 9, and 12 months following systemic initiation
  - The Kruskal-Wallis and Wilcoxon statistical tests compared the subgroups

Table 2. Patient Characteristics at Enrollment

Patient characteristic	(N=445)
Age (years) at enrollment	
Mean (SD)	30.8 (21.2)
Median (n)	24.0 (445)
Min – Max	0 - 86
Sex, n (%)	
Female	276 (62.0%)
Male	169 (38.0%)
Race-Ethnicity, n (%)	
Hispanic/Latino	88 (19.8%)
NH White	202 (45.4%)
NH Black	55 (12.4%)
NH Asian	63 (14.2%)
NH Other	19 (4.3%)
Missing	18 (4.0%)
IGA	
Mean (SD)	3.3 (0.5)
Median (n)	3.0 (445)
BSA	
Mean (SD)	26.1 (22.8)
Median (n)	18.0 (445)
BSA Category, n (%)	
Mild, >0% to <16%	212 (47.6%)
Moderate, 16% - 40%	148 (33.3%)
Severe, >40%	85 (19.1%)
Worst-Itch	
Mean (SD)	7.6 (2.3)
Median (n)	8.0 (243)

SD=standard deviation; NH=Non-Hispanic; IGA Investigator's Global Assessment or validated Investigator's Global Assessment of Atopic Dermatitis; BSA=Body Surface Area

Figure 2. Patient Disposition

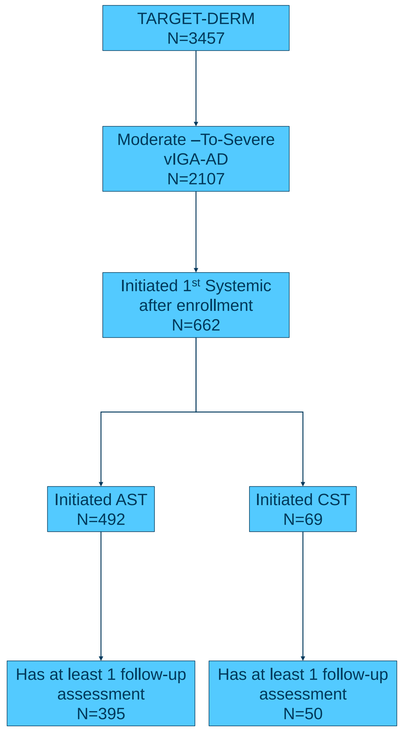

Table 3. Medication Utilization at Initiation

Medications	3 months (N=419)	6 months (N=394)	9 months (N=371)	12 months (N=342)
Any Conventional Systemic Therapy (CST), n (%)	35 (8.4%)	31 (7.9%)	29 (7.8%)	26 (7.6%)
Cyclosporine	10 (2.4%)	8 (2%)	8 (2.2%)	7 (2%)
Methotrexate	13 (3.1%)	12 (3%)	11 (3%)	10 (2.9%)
Mycophenolate mofetil	2 (0.5%)	2 (0.5%)	1 (0.3%)	1 (0.3%)
Prednisolone	2 (0.5%)	2 (0.5%)	2 (0.5%)	2 (0.6%)
Prednisone, unspecified	8 (1.9%)	7 (1.8%)	7 (1.9%)	6 (1.8%)
Any Advanced Systemic Therapy (AST), n (%)	384 (91.6%)	363 (92.1%)	342 (92.2%)	316 (92.4%)
Abrocitinib	3 (0.7%)	3 (0.8%)	3 (0.8%)	3 (0.9%)
Dupilumab	344 (82.1%)	327 (83%)	312 (84.1%)	296 (86.5%)
Tralokinumab	24 (5.7%)	20 (5.1%)	17 (4.6%)	11 (3.2%)
Upadacitinib	13 (3.1%)	13 (3.3%)	10 (2.7%)	6 (1.8%)

- Dupilumab was the most commonly used AST at each time point, with its use exceeding 82% throughout the 12-month follow-up period.
- 36.7% of patients treated with AST were also using concomitant topical corticosteroids or topical calcineurin inhibitors.

Figure 3. Therapeutic inertia among AST-treated Patients. Percentages of patients not achieving moderate and optimal treatment targets for skin clearance (IGA X BSA)

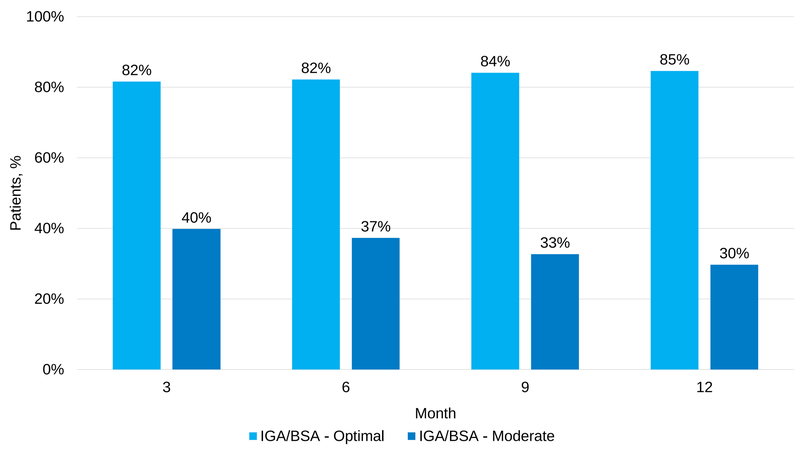

Figure 3b. Therapeutic inertia among AST-treated Patients. Percentages of patients not achieving moderate and optimal treatment targets for itch (WI-NRS)

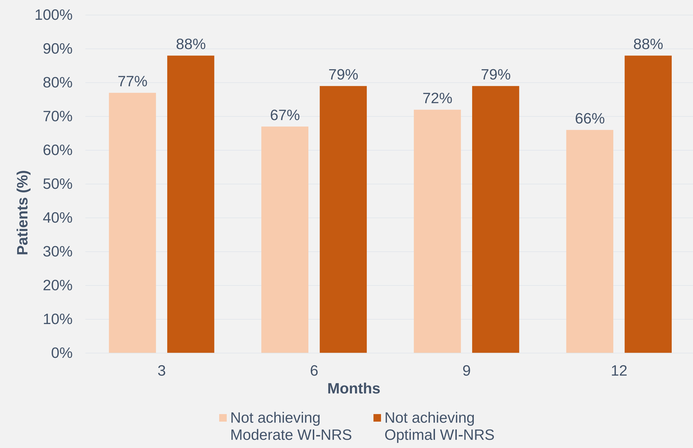

Table 4. Proportion of Patients Not Achieving Moderate Treatment Target by Systemic Treatment Subgroup

Outcome Measure	3 Months			6 Months			9 Months			12 Months		
	AST	CST	Overall	AST	CST	Overall	AST	CST	Overall	AST	CST	Overall
IGA and BSA n/N	78/196	13/22	91/218	44/118	8/15	52/133	35/107	12/19	47/126	27/91	6/13	33/104
%	39.8%	59.1%	41.7%	37.3%	53.3%	39.1%	32.7%	63.2%*	37.3%	29.7%	46.2%	31.7%
WI-NRS n/N	139/180	22/24	161/204	133/199	20/15	148/219	67/93	7/11	74/104	65/99	9/12	74/111
%	77.2%	91.7%	78.9%	66.8%	75.0%	67.6%	72.0%	63.6%	71.2%	65.7%	75.0%	66.7%

*P<0.05; **P<0.01; n/N=numerator/denominator

- At 6 months, 37% and ~ 67% of AST-treated patients had inadequate responses in terms of skin clearance and itch outcomes, respectively.
- At 12 months, these figures were approximately 30% and 66%, respectively.
- CST-treated patients showed a similar trend.

Table 5. Proportion of Patients Not Achieving Optimal Treatment Target by Systemic Treatment Subgroup

Outcome Metric	3 Months			6 Months			9 Months			12 Months		
	AST	CST	Overall	AST	CST	Overall	AST	CST	Overall	AST	CST	Overall
IGA and BSA n/N	160/196	20/22	180/218	97/118	13/15	110/133	90/107	18/19	108/126	77/91	12/13	89/104
%	81.6%	90.9%	82.6%	82.2%	86.7%	82.7%	84.1%	94.7%	85.7%	84.6%	92.3%	85.6%
Worst Itch n/N	159/180	19/24	178/204	158/199	18/20	176/219	91/115	12/14	103/129	159/180	19/24	178/204
%	88.3%	79.2%	87.3%	79.4%	90.0%	80.4%	79.1%	85.7%	79.8%	88.3%	79.2%	87.3%

n/N=numerator/denominator

- At 6 months, 82% and 79% of AST-treated patients did not meet optimal treatment targets in terms of skin clearance and itch outcomes, respectively.
- At 12 months, these figures were approximately 85% and 88%, respectively.
- CST-treated patients showed a similar trend.

Sensitivity Analysis

- For the subgroup of 198 patients who began advanced systemic therapy (AST) on or after September 1st, 2021, when additional AST options were approved and available in the market, the results were consistent with the overall cohort. This confirms that therapeutic inertia persists, even with the introduction of newer advanced systemic therapies.

Conclusion:

- The study reveals that a significant portion of moderate-to-severe AD patients fail to achieve adequate disease control with systemic therapies over 12 months, indicating a substantial presence of therapeutic inertia.
- These findings underscore the importance of adopting a treat-to-target approach, where therapy is adjusted or switched when adequate control is not achieved.

References

1. Silverberg JI, Gooderham M, Katoh N, Aoki V, Pink AE, Binamer Y, Rademaker M, Fomina D, Gutermuth J, Ahn J, Valenzuela F. Combining treat-to-target principles and shared decision-making: International expert consensus-based recommendations with a novel concept for minimal disease activity criteria in atopic dermatitis. Journal of the European Academy of Dermatology and Venereology. 2024 Jul 11.

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