

Introduction

- Epidermolysis bullosa acquisita (EBA) is a rare, acquired autoimmune blistering disease caused by autoantibodies against collagen VII (COL7), a protein crucial for dermoepidermal adhesion¹
- While the precise etiology of EBA remains unclear, medications and vaccines have been reported as potential triggers in limited studies²
- The spectrum of drug-associated EBA (DAEBA) has not been comprehensively characterised across large pharmacovigilance datasets

Aims

- To characterize the demographics, clinical outcomes, and implicated agents in DAEBA cases using multiple international pharmacovigilance databases, including the FDA Adverse Event Reporting System (FAERS), the Vaccine Adverse Event Reporting System (VAERS) and the Database of Adverse Event Notifications (DAEN)

Methods

- Cases of DAEBA were extracted from the FAERS, the VAERS, and the DAEN
- Inclusion criteria were EBA onset following monotherapy, reported as a single reaction term. Cases in which EBA was being actively treated were excluded
- Demographic data, reporter type, country of report, severity, outcomes, and implicated agents were recorded and categorised by pharmacological class

Results

Table 1: Baseline characteristics of EBA cases

Parameter	Number of cases
Total cases of EBA	58
Gender	Male: 28 (48.3%) Female: 23 (39.7%) Not reported: 7 (12.1%)
Age	Mean: 55.4 years (n=39) Range: 3 - 87 Not reported: 19 (26.5%)
Reporter	Healthcare professional: 42 (72.4%) Consumer: 9 (15.5%) Not specified: 7 (12.1%)
Severity of reaction	Serious: 50 (100%) Unreported: 8
Clinical outcome	Hospitalization: 19 (32.8%) Life threatening: 3 (5.2%) Disabled: 1 (1.7%) Death: 3 (5.2%) Other outcomes: 32 (55.17%)

Table 2: Overview of implicated medication triggers for EBA

Class of medication	Specific agent, n (cases)	Number of cases	
Antineoplastics/targeted therapy (13.8%)	Bortezomib/Thalidomide	1 (1.7%)	
	Erlotinib	1 (1.7%)	
	Osimertinib	1 (1.7%)	
	Pemetrexed	2 (3.4%)	
	Trametinib/naprafenib	1 (1.7%)	
	Sunitinib	1 (1.7%)	
	Methotrexate*	1 (1.7%)	
Neurologic/psychiatric (6.9%)	Carbamazepine	1 (1.7%)	
	Dimethyl fumarate	1 (1.7%)	
	Mirtazapine	1 (1.7%)	
	Divalproex/phenytoin	1 (1.7%)	
	Apalutamide	1 (1.7%)	
	Linagliptin	1 (1.7%)	
Endocrine/metabolic/GI (10.3%)	Semaglutide	1 (1.7%)	
	Esomeprazole	1 (1.7%)	
	Famotidine	1 (1.7%)	
	Etelcalcetide HCL	1 (1.7%)	
	Amoxicillin/APAP	2 (3.4%)	
	Amantadine/APAP	1 (1.7%)	
Analgesics/antibiotics/antivirals/antifungal (10.3%)	Oseltamivir/ibuprofen	1 (1.7%)	
	Fluconazole	2 (3.4%)	
	Immunologic (6.9%)	Human intravenous immunoglobulin (IVIg)	1 (1.7%)
		Drotecogin alpha*	1 (1.7%)
Cardiovascular/renal (6.9%)	Penicilliamine	1 (1.7%)	
	Aliskiren	1 (1.7%)	
	Valsartan	1 (1.7%)	
	Amlodipine/valsartan	1 (1.7%)	
	HCTZ/irbesartan	1 (1.7%)	
Vaccines (8.6%)	Pfizer COVID-19	4 (6.9%)	
	Gardasil HPV	1 (1.7%)	

Table 2: Overview of implicated medication triggers for EBA

Class of medication	Specific agent, n (cases)	Number of cases
Immunomodulators (24.1%)	Adalimumab	4 (6.9%)
	Etanercept	1 (1.7%)
	Infliximab	1 (1.7%)
	IFN-β-1b	2 (3.4%)
	Ustekinumab	2 (3.4%)
	Nemolizumab	1 (1.7%)
	Ocrelizumab	1 (1.7%)
	Risankizumab	1 (1.7%)
	Rituximab*	1 (1.7%)
	Atezolizumab	2 (3.4%)
Immunotherapy (13.8%)	Nivolumab	3 (5.2%)
	Tislelizumab	1 (1.7%)
	Pembrolizumab	1 (1.7%)
	Ipilimumab/nivolumab	1 (1.7%)

Discussion/Conclusion

- A total of 118 cases were identified, of which **58** met the eligibility criteria.
- **Demographic characteristics of the DAEBA patients:**
 - Mean patient age was 55.4 years, with males comprising 48.3% of cases
 - Healthcare providers reported 72.4% of cases
 - Most reactions were classified as serious; 32.8% required hospitalization, and three deaths occurred, which were linked to methotrexate, drotecogin alfa, and rituximab
- **Overview of implicated medication triggers:**
 - The most implicated drug classes were immunomodulatory biologic agents (24.1%) antineoplastics/targeted therapies (13.8%), and immune checkpoint inhibitors (13.8%)
 - Adalimumab was the most frequently implicated agent accounting for 6.9% of DAEBA cases
 - The Pfizer COVID-19 vaccine was implicated in four of the five vaccine-associated cases (80%)

Discussion/Conclusion

- Immunomodulatory biologic agents, antineoplastics, and ICIs were the most frequently implicated in DAEBA
- We propose that ICI-mediated T cell activation, or biologic/antineoplastic-mediated immune dysregulation may lead to a host B cell response that triggers the production of IgG, IgA and/or IgM antibodies, resulting in dermoepidermal detachment³. Cross-reactivity in previously sensitized individuals or molecular mimicry, where drugs resemble non-self antigens and trigger CD4⁺ T cell-mediated autoimmune responses, may also explain DAEBA⁴
- Although rare, prompt recognition and discontinuation of culprit agents are critical for improving outcomes

References

1. Kridin K, Kneiber D, Kowalski EH, Valdebran M, Amber KT. Epidermolysis bullosa acquisita: A comprehensive review. *Autoimmun Rev.* 2019;18(8):786-95.
2. Koga H, Prost-Squarcioni C, Iwata H, Jonkman MF, Ludwig RJ, Bieber K. Epidermolysis Bullosa Acquisita: The 2019 Update. *Front Med (Lausanne).* 2018;5:362.
3. Delbaldo C, Chen M, Friedli A, Prins C, Desmeules J, Saurat JH, et al. Drug-induced epidermolysis bullosa acquisita with antibodies to type VII collagen. *J Am Acad Dermatol.* 2002;46(5 Suppl):S161-4.
4. Verheyden MJ, Bilgic A, Murrell DF. A Systematic Review of Drug-Induced Pemphigoid. *Acta Derm Venereol.* 2020;100(15):adv00224.