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LETTER TO THE EDITOR

Immunomodulators and Antineoplastics Are Reported in Drug-Associated Epidermolysis Bullosa Acquisita Flares: A Retrospective Analysis of 58 Reported Cases Utilizing Multiple International Pharmacovigilance Databases

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Dear Editor,

Epidermolysis bullosa acquisita (EBA) is a rare, acquired autoimmune blistering disease developing due to autoantibodies against collagen VII (COL7), a protein crucial to maintaining skin integrity [1]. While the exact cause of EBA is unknown, medications and vaccines have been described as triggers in limited studies [2]. In this study, we utilize various pharmacovigilance databases, including the United States Food and Drug Administration Adverse Event Reporting System (FAERS), Vaccine Adverse Event Reporting System, and Database of Adverse Event Notifications, to identify drug-associated EBA (DAEBA) cases.

The databases were queried for all cases of DAEBA at any age, and patients who developed EBA following monotherapy and as one reaction term were included. Patients who were being treated for EBA were excluded. All data were reviewed by two authors, and duplicates were manually removed. Demographic information, including age, gender, reporter type, and country of report, as well as severity and clinical outcome, were extracted. Offending medications were identified and organized by medication class.

After initial data extraction, a total of 118 cases were identified, of which 58 met eligibility criteria (https://data.mendeley.com/datasets/p3y84zcnhx/1). Males comprised 48.3% of cases; there was a mean age of 55.4 years for all cases, and 72.4% of cases were reported by healthcare providers worldwide (Table 1). Most reactions were classified as "serious" with 32.8% of cases requiring hospitalization and three related deaths. Immunomodulatory biologic agents were the most commonly implicated agents (24.1%), followed by antineoplastics/targeted therapy (13.8%) and immune checkpoint inhibitors (ICIs) (13.8%) (Table 2). The three deaths were associated with methotrexate, drotecogin alpha, and rituximab use. The Pfizer COVID-19 vaccine was the most commonly implicated vaccine (4/5 cases).

We find a heterogeneous range of medications/vaccinations associated with DAEBA, with immunomodulatory biologic agents, antineoplastics, and ICIs being the most frequently implicated. 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 dermo-epidermal detachment [3]. 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 DAEBA [4].

Previous studies of drug-associated bullous pemphigoid suggested that antibiotics, anti-inflammatory drugs, and cardiovascular agents may bind to proteins in the lamina lucida of the basement membrane zone (BMZ), altering the antigenicity of the BMZ and triggering the production of anti-BMZ antibodies [4]. We find similarly implicated agents in DAEBA, whereby the offending agent may function as a hapten that alters the antigenicity of COL7 directly, releasing anti-COL7 antibodies [3].

Although the incidence of DAEBA is rare, prompt discontinuation of potential culprit medications is imperative for improved patient outcomes. Limitations of this analysis include the utilization of spontaneous adverse event reporting databases that may have incomplete and missing data, underreport total cases, and show a lack granular detail regarding diagnosis confirmation. The lack of specific AE severity scoring details and distinctions between de novo EBA versus EBA

TABLE 1 | Demographic parameters of acquired epidermolysis bullosa patients.

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 reported: 7 (12.1%)
Country of report	China: 7 (12.1%)
	Japan: 7 (12.1%)
	USA: 10 (17.2%)
	Germany: 5 (8.6%)
	France: 4 (6.9%)
	Italy: 3 (5.2%)
	Australia: 6 (10.3%)
	Spain: 2 (3.4%)
	United Kingdom: 1 (1.7%)
	Belgium: 1 (1.7%)
	Czech Republic: 1 (1.7%)
	Croatia: 1 (1.7%)
	Russia: 1 (1.7%)
	Not specified: 9 (15.5%)
Severity of reaction	Serious: 50 (86.2%)
	Not reported: 8 (13.8%)
Clinical outcome	Hospitalization: 19 (32.8%)
	Life threatening: 3 (5.2%)
	Disabled: 1 (1.7%)
	Death: 3 (5.2%)
	Other outcomes: 32 (55.17%)

Abbreviation: EBA, epidermolysis bullosa acquisita, USA, United States of America.

TABLE 2 | Overview of implicated medication triggers for acquired epidermolysis bullosa.

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%)
Immunotherapy (13.8%)	Atezolizumab	2 (3.4%)
	Nivolumab	3 (5.2%)
	Tislelizumab	1 (1.7%)
	Pembrolizumab	1 (1.7%)
	Ipilimumab/ nivolumab	1 (1.7%)
Antineoplastics/targeted therapy (13.8%)	Bortezomib/ Thalidomide	1 (1.7%)
	Erlotinib	1 (1.7%)
	Osimertinib	1 (1.7%)
	Pemetrexed	2 (3.4%)
	Trametinib/ naporafenib	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%)
Endocrine/metabolic/GI (10.3%)	Apalutamide	1 (1.7%)
	Linagliptin	1 (1.7%)
	Semaglutide	1 (1.7%)
	Esomeprazole	1 (1.7%)
	Famotidine	1 (1.7%)
	Etelcalcetide HCL	1 (1.7%)

(Continues)

TABLE 2 | (Continued)

Class of medication	Specific agent, *n* (cases)	Number of cases
Analgesics/antibiotics/antivirals/antifungal (10.3%)	Amoxicillin/APAP	2 (3.4%)
	Amantadine/APAP	1 (1.7%)
	Oseltamivir/ibuprofen	1 (1.7%)
	Fluconazole	2 (3.4%)
Immunologic (6.9%)	Human intravenous immunoglobulin (IVIg)	1 (1.7%)
	Drotecogin alpha*	1 (1.7%)
	Penicillamine	1 (1.7%)
Cardiovascular/renal (6.9%)	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%)

Abbreviations: APAP, acetaminophen; GI, gastrointestinal; HCL, hydrochloric acid; HCTZ, hydrochlorothiazide; HPV, human papillomavirus; IFN, interferon; IVIG, intravenous immunoglobulin.
*Three deaths were associated with drotecogin alpha, methotrexate, and rituximab use.

flares occurring in patients taking these medications also limit generalizability. Providers and patients can be aware that many drug classes, particularly immunomodulators and antineoplastics, may be associated with DAEBA and can be potentially discontinued or switched to alternative agents/anti-tumor therapy during disease flares when feasible.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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