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1 **Drug-induced skin ulcers: a disproportionality analysis from the WHO**

2 **pharmacovigilance database**

3 **Short running title: Drug-induced skin ulcer**

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41 Skin ulcerations have occasionally been reported as adverse drug reactions (ADR).¹
42 However, to our knowledge, no pharmacovigilance study has been performed to date, and
43 little is known about drug-related skin ulcers.
44 We therefore performed combined disproportionality analyses using data from VigiBase®, the
45 World Health Organization pharmacovigilance database, and from the biomedical literature
46 through Medline, to identify pharmacological classes suspected of inducing skin ulcers.^{2,3}
47 Then, all disproportionality signals were independently reviewed by a committee of experts in
48 pharmacology and dermatology, and selected according to their clinical relevance, the
49 strength of evidence and previous knowledge of possible associations (supplementary
50 method, available on Mendeley 10.17632/sgnzs8k9tt.1).⁴
51 From the 21,421,352 cases available at the time of extraction (2020-03-03), we identified
52 19,887 reports of ‘skin ulcer’, 4,440 of ‘decubitus ulcer’, 596 of ‘diabetic ulcer’, 103 of
53 ‘varicose ulceration’ and 79 of ‘ischemic skin ulcer’. Sixty-one drugs displayed a
54 disproportionality signal for both ‘skin ulcer’ and at least one other specific skin ulcer term
55 (Supplementary Figure 1, available on Mendeley 10.17632/sgnzs8k9tt.1). Among 814
56 records of chemically-induced skin ulcers identified in the literature after screening titles and
57 abstracts, 241 reports regarding 59 drugs were selected, among which 10 had a
58 disproportionality signal.
59 Among the 61 drugs selected for signal validation, 22 were excluded for obvious indication or
60 protopathic bias, or were combined substances (Supplementary Table 1, available on
61 Mendeley 10.17632/sgnzs8k9tt.1). Then, after retrieving references databases, FDA/EMA
62 labels and safety alerts, 21 drugs were considered as “already known” and the plausibility of
63 the remainig 19 drugs was assesed through discussion during expert meeting based on cases
64 analyses, potential bias and pharmacological mechanisms (Supplementary Table 2 and 3,
65 available on Mendeley 10.17632/sgnzs8k9tt.1). Finally, 13 drugs were considered as having

66 potential signals for skin ulcer: three protein kinase inhibitors (afatinib, ibrutinib, tofacitinib),
67 two immunomodulators (thalidomide and lenalidomide), two interferons (alpha and beta), one
68 bisphosphonate (alendronic acid), leflunomide, rofecoxib, mitomycin, ocrelizumab and
69 digoxin (Table 1 and Supplementary Table 4, available on Mendeley 10.17632/sgnzhg8k9tt.1).
70 Four main mechanisms have been proposed as being implicated in the pathogenesis of
71 iatrogenic skin ulcers: angiogenesis inhibition, direct skin toxicity and decreased skin
72 perfusion through vasoconstriction or increased blood viscosity. ¹ Except for ocrelizumab, for
73 which we did not find any pharmacological hypothesis, all identified drugs could be related to
74 these main mechanisms (Figure 2 and Supplementary Table 5, available on Mendeley
75 10.17632/sgnzhg8k9tt.1).

76 This study has limitations. First, selective reporting of ADR in pharmacovigilance databases,
77 inherent to the spontaneous nature of notifications, may distort the associations found in this
78 study. ⁵ In addition, the development of a skin ulcer is often multifactorial, and clear causality
79 with drug exposure might be difficult to assess given the high rate of missing clinical data.

80 To the best of our knowledge, this is the first pharmacovigilance study identifying iatrogenic
81 etiologies of skin ulcers. The identified signals represent plausible ADR by considering the
82 understanding of iatrogenic skin ulcers, biological and pharmacological drug activity and
83 reported cases characteristics. However, they have yet to be evaluated by purpose-designed
84 epidemiological studies.

85

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88 Alpes University Hospital) for critically editing our manuscript.

89 The data supplied to VigiBase come from a variety of sources and the likelihood of a causal
90 relationship is not the same in all reports. The information does not represent the opinions of
91 the UMC or the World Health Organization.

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109 **Figure legends**

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111 **Figure 1.** Schematic representation of the mechanisms of iatrogenic skin ulcers. Drugs
 112 previously unknown to be associated with skin ulcers are in orange. G-protein-coupled
 113 receptors (GPCR); endothelial growth factor (EGF); fibroblast growth factor (FGF); platelet-
 114 derived growth factor (PDGF); vascular endothelial growth factor (VEGF); membrane
 115 glucocorticoid receptor (mbGC-R).

116

117 **Table**

118 Table 1. Results of the disproportionality analyses. The lower boundary of the Information
 119 Component (IC025) in the WHO pharmacovigilance database and in Medline (if significant)
 120 is provided for each drug. Warnings about skin ulcers, retrieved from references databases,
 121 EMA, FDA summary product characteristics are indicated. New safety signals are in bold.
 122 SDR: signal of disproportionate reporting.

123

Drug classes	Drugs	SDR in WHO pharmacovigilance database	SDR in Medline	Known associations
<i>Protein kinase inhibitors</i>	Sorafenib	2.19		Ulceration [§]
	Sunitinib	1.99		Cracking of skin [§]
	Afatinib	1.02		
	Erlotinib	2.12		Skin fissure [§]
	Ibrutinib	2.10		
	Cabozantinib	4.63		Skin ulcer [¶]
	Lenvatinib	2.56		Impaired wound healing [±]
	Pazopanib	1.10		Skin ulcer [§]
	Tofacitinib	0.51		
	Regorafenib	0.97		Impaired wound healing [±]
	Ponatinib	0.77		Skin pain
<i>mTOR inhibitors</i>	Everolimus	1.15		Impaired wound healing [±]
	Sirolimus	1.66		Impairment of Wound Healing [§]
<i>Antimetabolites</i>	Methotrexate	1.52	1.84	Skin ulcer [§]
	Hydroxycarbamide	5.85	5.95	Leg ulcer [§]
	Teriflunomide	0.02		
<i>Calcineurin inhibitor</i>	Tacrolimus	0.16		Skin ulcer [§]
<i>Immunomodulators</i>	Lenalidomide	0.19		
	Thalidomide	0.15		
<i>Antitumor antibiotic</i>	Mitomycin	2.52	0.39	
<i>CD-20 antibody</i>	Ocrelizumab	0.12		
<i>Bisphosphonates</i>	Alendronic acid	1.49		
<i>VEGF inhibitors</i>	Bevacizumab	1.33		Wound healing complications [§]
<i>TNF alpha inhibitors</i>	Adalimumab	0.65		Signal of skin ulcer [¥]
	Etanercept	1.11		Leg ulcer [¶]
<i>Interferons</i>	Interferon beta	0.14	1.59	
	Interferon alpha	0.99	0.81	
<i>Cardiac glycosides</i>	Digoxin	0.77		
<i>Non-opioid analgesic</i>	Ziconotide	0.06		Skin ulcer [§]
<i>Cox 2 inhibitors</i>	Rofecoxib	0.96		
<i>Glucocorticoids</i>	Prednisone	1.38		Impairs wound healing [§]

<i>SGLT-2 inhibitors</i>	Canagliflozin	4.41		Ulcers of the lower limbs [§]
<i>Potassium channel activators</i>	Nicorandil	5.02	4.85	Skin ulceration [§]
<i>Opiate analgesics</i>	Pentazocine	1.13	3.75	Ulceration of the skin [§]

124 §: FDA summary of product characteristics; ¶: EMA summary of product characteristics; ±: Micromedex
125 database; ¥: PRAC safety signal assessment.

