Specific-class Skin Side-effects of Drugs Might Compromise Blinding in Randomized Controlled Trials

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Randomized controlled trials (RCTs) are the gold standard for high-quality evidence-based medicine. Double-blinding in RCTs allows for avoiding performance bias, whereas absence of blinding exaggerates treatment effects by 14–35% compared with double-blinding (1, 2). Therefore, maintaining blinding is crucial, especially when the endpoints of studies are subjective outcomes (3, 4). The "open" or "blinded" design is usually reported and discussed in the limitation sections of studies, but the risk of unblinding during the trial is rarely reported (3, 4). However, except for new drugs, the side-effects of which are still not known (5, 6), several drugs induce specific-class side-effects (SCSEs), especially skin effects; hence the participants taking the drug(s) during a trial can be detected easily.

To highlight this important issue, we chose 2 classes of molecules (acitretin and isotretinoin for oral drugs, imiquimod for topical drugs) with well-known SCSEs (mainly cutaneous and mucosal xerosis/local inflammatory reaction) and performed a systematic review to deduce the risk of unblinding in RCTs of these drugs.

MATERIALS AND METHODS

Trials comparing acitretin, isotretinoin and imiquimod with placebo or an active comparator were selected; which were included in the electronic databases MEDLINE and CENTRAL during 1982–2016 with at least 1 actor reported to be blinded (patient, care provider or outcome assessor). Extracted data included items related to blinding, the frequency of SCSEs and the primary outcomes of trials that we classified as: (*i*) objective outcomes (such as complete regression of lesions on imaging), (*ii*) subjective outcomes (pain or quality of life for example), and (*iii*) unclear (7).

Statistical analysis

Descriptive statistics are expressed with number (%) for categorical data. Meta-analysis of adverse events was performed by computing odds ratios (ORs) with use of fixed-effects modelling. ORs and 95% confidence intervals (95% CI) were calculated. Statistical analyses involved use of SAS 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

From the 486 articles screened, 75 trials were included (21 for acitretin, 25 for isotretinoin and 29 for imiquimod)

that concerned 3 main conditions: inflammatory diseases (n=54), skin cancers (n=16), and non-skin cancers (n=5).

In 61% of RCTs, care providers and patients were reported to be blinded (16/21, 18/25 and 12/29 for acitretin, isotretinoin and imiquimod, respectively), and outcome assessors were reported to be blinded in all trials. In 4 RCTs of imiquimod, the authors only briefly mentioned "difficulties" with unblinding.

Adverse events were reported in 80% of RCTs overall (n=60). As expected, SCSEs included dryness and cheilitis for retinoids (reported in 67% of RCTs assessing acitretin and 56% of isotretinoin) and local irritation, inflammation and wounds for imiquimod (reported in 83% of RCTs). Forest plot analysis of the 40 (53%) RCTs that provided details on adverse effects showed that the rates of SCSEs were always much higher in the experimental than control groups (**Fig. 1**).

Subjective primary outcomes were used in 53% of RCTs (16/21 for RCTs of acitretin, 12/25 isotretinoin and 12/29 imiquimod), and objectives outcomes represented 16% of RCTs (1/21, 6/25 and 5/29, respectively); the others were considered unclear. For conditions, subjective and objective outcomes were used in 78.0% (32/41) and 9.8% (4/41), respectively, of RCTs of inflammatory diseases, 25% (4/16) and 56.3% (9/16) of RCTs of skin cancers and 0/4 and 4/4 of RCTs of non-skin cancers; the others were unclear. No guarantee was mentioned to maintain blinding despite the probable unblinding linked to SCSEs of drugs.

DISCUSSION

By focusing on 3 different molecules, this study shows that a high frequency of SCSEs that are visible and that occur very rarely in the control group could lead to unblinding in RCTs. Indeed, when SCSEs occurred, they allowed for the outcome assessors to easily guess to which treatment group patients were assigned. If the endpoint of the trial is subjective, then the outcome assessor might be influenced in the evaluation of treatment efficacy, which leads to a bias, as in open-label RCTs (3, 4, 7). In most cases, primary outcomes were subjective in RCTs of these 3 molecules.

As dermatologists, we considered only drugs with cutaneous SCSEs because they are visible and easily recognizable. For some, such as imiquimod, local irritation

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Study	Ac Events	itretin Total		ontrol Total	Odds Ratio	OR	95%-CI	Weigh
Schröder, 1989	10	15	4	15		5.50	[1.15; 26.41]	7.09
Tanew, 1991	19	23	9	25		8.44	[2.18; 32.66]	9.49
Bavinck, 1995	15		5				[2.34; 47.20]	7.69
Gaeta, 2000	11		2				[1.15; 73.24]	4.09
Verfaille, 2007	13		5				[1.66: 45.21]	6.39
	18		с 9					
Gisondi, 2008							[2.40; 70.46]	6.0%
Caproni, 2009	27		9				[5.05; 87.37]	8.5
Ioannides, 2010	23		4				[1.78; 26.71]	9.49
Kadakia, 2012	26	35	8	35		9.75	[3.26; 29.12]	14.49
Akçali, 2014	21	25	8	21	<u> </u>	8.53	[2.14; 34.09]	9.0
Wu, 2015	50	57	19	58			[5.60; 38.39]	18.6
Random effects model	I	287		263		10.31	[6.81; 15.61]	100.09
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0).99						
					0.1 0.51 2 10			
					Control Acitretin			
Of the state	Imiqu			ontrol		0.0	05% 01	M/- ! - !
Study	Events	lotal E	vents	Total	Odds Ratio	OR	95%-CI	weigi
Syed, 2000	27	30	5	30		45.00	[9.73; 208.08]	3.19
Stockfleth, 2002	21	25	4	11			[1.80; 46.83]	2.7
Seeberger, 2003	10	12	1	3			0.58; 171.20]	0.9
Schulze, 2005	27	84	1	82			[5.07; 290.53]	1.8
Ulrich, 2007	5	29	1	14			[0.29; 25.71]	1.5
	9		5					
Butler, 2009		12		12			[0.74; 23.91]	2.4
Gebauer, 2009	95	120	4	29			[7.57; 74.54]	5.3
Morales Toqueno, 2010	28	35	9	35			[3.76; 35.51]	5.5
Grimm, 2012	23	25	9	24			[3.63; 101.26]	2.6
Goldenberg, 2013	8	10	2	10		16.00	[1.79; 143.15]	1.5
Gupta, 2013	14	28	5	25		4.00	[1.17; 13.66]	4.7
Hung, 2014	27	30	15	61		27.60	[7.32; 104.10]	4.1
Kumar, 2014	39	44	12	45			[6.85; 67.18]	5.4
Swanson, 2014	278	318	64	161	<u> </u>		[6.67; 16.65]	23.4
Dytoc, 2015	10	13	3	12			[1.59; 62.73]	2.2
Lecluse, 2015	164	198	87	403				
Hung, 2016	32	40	21	403 120			[11.29; 27.18] [7.62; 46.69]	24.7 8.1
•								
Random effects model Heterogeneity: $I^2 = 6\%$, τ^2		1053 p = 0.38		1077 Г	→ → →	14.16 [10.75; 18.66]	100.0
meterogeneity: $I^- = 6\%, \tau^-$				0.0	1 0.1 1 10 100			
meterogeneity: $I^{-} = 6\%$, τ^{-}	,				1 0.1 1 10 100			
neterogeneity: r = 6%, τ					Control Imiquimod			
	Isotreti Events 1			ntrol		OR	95%-C	Weig
Study	Isotreti Events 1	Total E	vents 1	ntrol Total	Control Imiquimod			
Study Pigatto, 1986	Isotreti Events 1	Total E	vents 1	ntrol Total 12	Control Imiquimod	4.00	[0.73; 21.84]	2.3
Study Pigatto, 1986 Oslen, 1989	Isotreti Events 1 8 7	12 9	vents 1 4 2	ntrol Total 12 8	Control Imiquimod	4.00 10.50	[0.73; 21.84 [1.11; 98.91]	2.3 1.3
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994	Isotreti Events 1 8 7 8	Total E 12 9 10	vents 1 4 2 3	ntrol Total 12 8 10	Control Imiquimod	4.00 10.50 9.33	[0.73; 21.84 [1.11; 98.91 [1.19; 72.99	2.3 1.3 1.6
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004	Isotreti Events 1 8 7 8 20	Total E 12 9 10 28	vents 1 4 2 3 9	ntrol Total 12 8 10 25	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44	[0.73; 21.84 [1.11; 98.91 [1.19; 72.99 [1.40; 14.14	2.3 1.3 1.6 5.0
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007	Isotreti Events 1 8 7 8 20 23	Total E 12 9 10 28 24	vents 1 4 2 3 9 4	ntrol Fotal 12 8 10 25 25	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14 [2.48; 1168.50]	2.3 1.3 1.6 5.0 1.3
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007	Isotreti Events 1 8 7 8 20	Total E 12 9 10 28 24 340	vents 1 4 2 3 9 4 97	ntrol Total 12 8 10 25	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44	[0.73; 21.84 [1.11; 98.91 [1.19; 72.99 [1.40; 14.14	2.3 1.3 1.6 5.0 1.3
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010	Isotreti Events 1 8 7 8 20 23	Total E 12 9 10 28 24	vents 1 4 2 3 9 4	ntrol Fotal 12 8 10 25 25	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14 [2.48; 1168.50]	2.3 1.3 1.6 5.0 1.3 46.3
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010	Isotreti Events 1 8 7 8 20 23 280	Total E 12 9 10 28 24 340	vents 1 4 2 3 9 4 97	ntrol Total 12 8 10 25 25 233	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [⁷ 6.54	[0.73; 21.84] [1.11; 98.91] [1.19; 72.99 [1.40; 14.14] 12.48; 1168.50 [4.47; 9.58] [0.81; 18.18]	2.3 1.3 1.6 5.0 1.3 46.3 2.8
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011	Isotreti Events 1 8 7 8 20 23 280 16 15	Total E 9 10 28 24 340 21 20	vents 1 4 2 3 9 4 97 5 7	ntrol Fotal 12 8 10 25 25 233 11 19	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7 6.54 3.84 5.14	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14 [2.48; 1168.50 [4.47; 9.58 [0.81; 18.18 [1.30; 20.36]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011 Olguin-Garcia, 2013	Isotreti Events 1 8 7 8 20 23 280 16 15 12	Total E 12 9 10 28 24 340 21 20 16	vents 1 4 2 3 9 4 97 5 7 4	ntrol Fotal 12 8 10 25 25 233 11 19 15	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7 6.54 3.84 5.14 8.25	[0.73; 21.84] [1.11; 98.91] [1.19; 72.99] [1.40; 14.14] 12.48; 1168.50 [4.47; 9.58] [0.81; 18.18] [1.30; 20.36] [1.65; 41.25]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011 Olguin-Garcia, 2013 Rademaker, 2014	Isotreti Events 7 8 7 8 20 23 280 16 15 12 12	Total E 12 9 10 28 24 340 21 20 16 29	vents 1 4 2 3 9 4 97 5 7 4 3	ntrol Total 12 8 10 25 25 233 11 19 15 29	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7 6.54 3.84 5.14 8.25 14.18	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14 12.48; 1168.50 [4.47; 9.58 [0.81; 18.18 [1.30; 20.36] [1.65; 41.25 [3.46; 58.15]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6 3.4
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011 Olguin-Garcia, 2013 Rademaker, 2014 Tan, 2014	Isotreti Events 1 8 7 8 20 23 280 16 15 12 18 89	Total E 12 9 10 28 24 340 21 20 16 29 133	vents 1 4 2 3 9 4 97 5 7 4 3 34	ntrol Total 12 8 10 25 233 11 19 15 29 133	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7 6.54 3.84 5.14 8.25 14.18 5.89	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99] [1.40; 14.14 [2.48; 1168.50 [4.47; 9.58] [0.81; 18.18] [1.30; 20.36 [1.65; 41.25] [3.46; 58.15] [3.46; 58.15]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6 3.4 2.8 3.4 2.8 3.4 2.8
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004	Isotreti Events 7 8 7 8 20 23 280 16 15 12 12	Total E 12 9 10 28 24 340 21 20 16 29	vents 1 4 2 3 9 4 97 5 7 4 3	ntrol Total 12 8 10 25 25 233 11 19 15 29	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7 6.54 3.84 5.14 8.25 14.18	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14 12.48; 1168.50 [4.47; 9.58 [0.81; 18.18 [1.30; 20.36] [1.65; 41.25 [3.46; 58.15]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6 3.4 2.3 9
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011 Olguin-Garcia, 2013 Rademaker, 2014 Tan, 2014 Gahalaut, 2014 Random effects model	Isotreti Events 7 8 7 8 20 23 280 16 15 12 18 89 24	Total E 12 9 10 28 24 340 21 20 16 29 133 33 675	vents 1 4 2 3 9 4 97 5 7 4 3 34	ntrol Total 12 8 10 25 233 11 19 15 29 133	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [7 6.54 3.84 5.14 8.25 14.18 5.89	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99] [1.40; 14.14 [2.48; 1168.50 [4.47; 9.58] [0.81; 18.18] [1.30; 20.36 [1.65; 41.25] [3.46; 58.15] [3.46; 58.15]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6 3.4 23.9 5.9
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011 Olguin-Garcia, 2013 Rademaker, 2014 Tan, 2014 Gahalaut, 2014	Isotreti Events 7 8 7 8 20 23 280 16 15 12 18 89 24	Total E 12 9 10 28 24 340 21 20 16 29 133 33 675	vents 1 4 2 3 9 4 97 5 7 4 3 34	ntrol fotal 12 8 10 25 25 233 11 19 15 29 133 32 552	Control Imiguimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [6.54 3.84 5.14 8.25 14.18 5.89 5.87 6.52	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14] [2.48; 1168.50 [4.47; 9.58 [0.81; 18.18 [1.30; 20.36 [1.65; 41.25 [3.46; 58.15 [3.46; 10.02 [2.01; 17.11]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6 3.4 23.9 5.9
Study Pigatto, 1986 Oslen, 1989 Ertl, 1994 Georgala, 2004 Oprica, 2007 Gollnick, 2010 Bagatin, 2010 Mortazavi, 2011 Olguin-Garcia, 2013 Rademaker, 2014 Tan, 2014 Gahalaut, 2014 Random effects model	Isotreti Events 7 8 7 8 20 23 280 16 15 12 18 89 24	Total E 12 9 10 28 24 340 21 20 16 29 133 33 675	vents 1 4 2 3 9 4 97 5 7 4 3 34	ntrol Total 12 8 10 25 25 233 11 19 15 29 133 32	Control Imiquimod Odds Ratio	4.00 10.50 9.33 4.44 120.75 [6.54 3.84 5.14 8.25 14.18 5.89 5.87 6.52	[0.73; 21.84 [1.11; 98.91] [1.19; 72.99 [1.40; 14.14] [2.48; 1168.50 [4.47; 9.58 [0.81; 18.18 [1.30; 20.36 [1.65; 41.25 [3.46; 58.15 [3.46; 10.02 [2.01; 17.11]	2.3 1.3 1.6 5.0 1.3 46.3 2.8 3.6 2.6 3.4 23.9 5.9

Fig. 1. Forest plots describing the occurrence of specific class side-effects (SCSE) in experimental and control groups of randomized controlled trials of acitretin, isotretinoin and imiquimod. (References are available in Appendix S1) "Events" are the number of patients with specific class side-effects, and "Total" represents the number of patients included in the trial. Control includes placebo (for 25/40 trials, 62.5%) or active comparator (for 14/40 trials, 35%) and in one trial (1/40, 2.5%), experimental treatment was compared with both placebo and active comparator. 95% CI: 95% confidence interval.

is a side-effect and is directly linked to the treatment effect (8). However, several drugs might induce SCSEs that are less visible, such as a decrease in cardiac frequency (e.g. RCTs of propranolol) or biologic side-effects (e.g. increase in liver enzyme levels after methotrexate treatment). To maintain blinding, protocols elaborate specific procedures: assessing efficacy by using photographs as in the RCT on propranolol in infantile haemangiomas (9) or using 2 independent assessors (1 for efficacy and 1 for biologic side-effects) in the trial on methotrexate for spontaneous chronic urticaria (10). Finally, some adverse events, such as stomach pain or headaches, are frequently reported in experimental groups, but also in

placebo groups in RCTs (11-13) and therefore are less likely to induce unblinding.

In conclusion, in RCTs assessing drugs with SCSEs, objective outcomes are recommended (as in open-label RCTs) to avoid risk of unblinding; otherwise, measures must be implemented so that outcome assessors can be independent (photographs, active placebo, makeup). When such strategies cannot be implemented, transparency in lack of blinding is mandatory.

The authors have no conflicts of interest to declare.

REFERENCES

- 1. Bello S, Moustgaard H, Hróbjartsson A. Unreported formal assessment of unblinding occurred in 4 of 10 randomized clinical trials, unreported loss of blinding in 1 of 10 trials. J Clin Epidemiol 2017; 81: 42-50.
- 2. Savović J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials._Ann Intern Med 2012; 157: 429-438.
- 3. Boutron I, Estellat C, Guittet L, Dechartres A, Sackett DL, Hróbjartsson A, et al. Methods of blinding in reports of randomized controlled trials assessing pharmacologic treatments: a systematic review. PloS Med 2006; 3: e425.
- 4. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. Int J Epidemiol 2014; 43: 1272-1283.
- 5. Lacouture ME, Sibaud V, Anadkat MJ, Kaffenberger B, Leventhal J, Guindon K, et al. Dermatologic adverse events associated with selective fibroblast growth factor receptor inhibitors: overview, prevention, and management guidelines. Oncologist 2021; 26: e316-e326.
- 6. Khalil S, Bardawil T, Stephan C, Darwiche N, Abbas O, Kibbi AG, et al. Retinoids: a iourney from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. J Dermatolog Treat 2017; 28: 684-696.
- 7. Moustgaard H, Bello S, Miller FG, Hróbjartsson A. Subjective and objective outcomes in randomized clinical trials: definitions differed in methods publications and were often absent from trial reports._J Clin Epidemiol 2014; 67: 1327-1334.
- 8. Ueyama A, Yamamoto M, Tsujii K, Furue Y, Imura C, Shichijo M, et al. Mechanism of pathogenesis of imiguimod-induced skin inflammation in the mouse: a role for interferon-alpha in dendritic cell activation by imiquimod. J Dermatol 2014; 41: 135-143.
- 9. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015; 372: 735-746.
- 10. Leducq S, Samimi M, Bernier C, Soria A, Amsler E, Staumont-Sallé D, et al. Efficacy and safety of methotrexate versus placebo as add-on therapy to H1 antihistamines for patients with difficult-to-treat chronic spontaneous urticaria: a randomized,

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controlled trial. J Am Acad Dermatol 2020; 82: 240-243.

- 11. Howick J, Webster R, Kirby N, Hood K. Rapid overview of systematic reviews of nocebo effects reported by patients taking placebos in clinical trials. Trials 2018; 19: 674.
- 12. Golder S, Loke Y, McIntosh HM. Poor reporting and inadequate

searches were apparent in systematic reviews of adverse effects. J Clin Epidemiol 2008; 61: 440–448. 13. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety

results in published reports of randomized controlled trials. Arch Intern Med 2009; 169: 1756-1761.