See related commentary on pg 16

Comparative Effectiveness of Topical Drugs in Dermatologic Priority Diseases: Geometry of Randomized Trial Networks

Annabel Maruani[1,2], Mahtab Samimi[1,3], Gérard Lorette[1,3] and Laurence le Cleach[4,5]

Among the 100 initial priority topics for comparative effectiveness research, three concern topical drugs in the following dermatologic diseases: psoriasis, chronic lower-extremity wounds (CLEWs), and acne vulgaris (AV). Our objective was to explore the geometry of the corresponding networks of randomized controlled trials (RCTs). We performed a review of RCTs on topical drugs in psoriasis, CLEWs, and AV. We searched MEDLINE, Embase, and CENTRAL for published trials from 2007 to 2012 and ClinicalTrials.gov for unpublished trials registered since 2011. RCTs comparing at least one topical treatment with any active or inactive comparator, regardless of RCT design and outcomes, were eligible. We produced network graphs (each node representing a treatment and links between nodes representing trials) and tested for co-occurrence (preference or avoidance of specific comparisons). We included 60 RCTs on psoriasis (14,255 patients) and 19 registered RCTs, 50 of CLEWs (5,916 patients) and 7 registered RCTs, and 90 of AV (22,984 patients) and 21 registered RCTs. Head-to-head comparisons were made in 78%, 32%, and 57% of published RCTs of these conditions, respectively. The co-occurrence test suggested that no specific head-to-head comparison was significantly preferred or avoided (P-value = 0.53, 0.20, and 0.57, respectively). This study has limitations, the main being that the search period was restricted to 5 years. In conclusion, more comparative effectiveness trials are needed for CLEWs, for which head-to-head comparisons are fewer than those for psoriasis and AV.

Journal of Investigative Dermatology (2015) **135,** 76–83; doi:10.1038/jid.2014.296; published online 28 August 2014

INTRODUCTION

Comparative effectiveness research (CER) fosters ''the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in real world settings'' (Sox and Greenfield, 2009; Nambudiri and Qureshi, 2013). The Institute of Medicine for the CER initiative, launched in 2009, established 100 initial priority topics. Topics were ranked by quartiles. Among them, three directly concerned the assessment of topical treatments in dermatologic conditions: psoriasis (2nd quartile), chronic lower-extremity wounds (CLEWs, 3rd quartile), and acne vulgaris (AV) (4th quartile) (IOM (Institute of Medicine), 2009).

Topical drugs are widely used in dermatology for most skin conditions such as inflammatory and infectious cutaneous diseases. They are the mainstay of treatment for most patients with mild to moderately severe conditions, for which they can be used alone or in association with a cosmetic product or a combination of topical treatments. For moderate-to-severe conditions, systemic drugs are required and are often combined with topical drugs (Lapolla *et al.*, 2011; Seité *et al.*, 2012; Kivelevitch *et al.*, 2013). A multitude of topical drugs are in the market and have a real economic impact. For instance, the estimated market value of topical agents for psoriasis in 2008 was $850 million (Melnikova, 2009). When multiple treatments are available for a given condition, dermatologists and patients should be able to identify which treatments work best, and decision making should be informed by evidence from randomized controlled trials (RCTs) (Wan *et al.*, 2012; Zenilman *et al.*, 2013).

In this framework, comparisons of RCTs investigating different interventions for a given condition constitute a trial network (Salanti *et al.*, 2008). Examining such a network allows for assessing which topical treatments have been compared head to head and which have been compared with an inactive control (vehicle or placebo) or a common

[1]Department of Dermatology, University François Rabelais Tours, CHRU Tours, University Hospital Center of Tours, Trousseau Hospital, Tours, France; [2]INSERM U930, Paris, France; [3]ISP 1282, UMR INRA-University François Rabelais, Paris, France; [4]French Cochrane Centre, Paris, France and [5]Hospital Créteil, Department of Dermatology, Créteil, France

Correspondence: Annabel Maruani, Department of Dermatology, University Hospital Center of Tours, Trousseau Hospital, University François Rabelais Tours, CHRU Tours, 37044, Tours, France.
E-mail: annabel.maruani@univ-tours.fr

Abbreviations: AV, acne vulgaris; CER, comparative effectiveness research; CLEW, chronic lower-extremity wound; PIE, probability of interspecific encounter; RCT, randomized controlled trial

Received 31 March 2014; revised 4 June 2014; accepted 11 June 2014; accepted article preview online 21 July 2014; published online 28 August 2014

comparator (e.g., a systemic treatment) (Mills *et al.*, 2013). It also allows for assessing the overall amount of evidence in the trial network and whether some comparisons are overrepresented.

We aimed to perform a network analysis of RCTs on topical drugs for psoriasis, CLEWs, and AV published during a recent 5-year period. In particular, we sought to determine the number of topical drugs used for each of these conditions, whether some are disproportionately preferred or neglected in clinical trials, and the proportion of trials using inactive comparators so as to detect gaps in the existing evidence that should dictate the future research agenda (Ioannidis and Karassa, 2010). Moreover, we aimed to compare this published evidence with trials registered in ClinicalTrials.gov not yet published to determine whether recommendations for CER have been taken into account.

RESULTS

Search results for psoriasis, CLEWs, and AV

We found 60 published trials on psoriasis from 361 initially searched (14,255 patients, range 5–2,920 per trial), with 19 trials from 117 registered at ClinicalTrials.gov. We included 50 published trials on CLEWs from 169 selected (5,916 patients, range 19–953 per trial), with 7 trials from 124 registered at ClinicalTrials.gov. We included 90 published trials on AV from 437 selected (22,984 patients, range 13–3,010 per trial), with 21 trials from 63 registered at ClinicalTrials.gov (See Supplementary File S1 online).

Characteristics of trials

Trials of psoriasis. The 60 reports on RCTs described 31 different topical drugs that we classified into 12 therapeutic classes (Table 1; Supplementary File S3 online): Thirteen reports (22%) described two-arm studies against an inactive control only and 25 (42%) reported at least one arm compared with an inactive control (Figure 1a). In total, 21 interventions were assessed: 13 topical drugs alone, 5 combinations of topical drugs, 1 combination of a topical and a systemic drug, 1 with a no treatment arm, and 1 inactive control. Because of multi-arm trials, we found 100 randomized comparisons of the 21 interventions. The network of trials had considerable diversity (probability of interspecific encounter (PIE) = 0.88). The most-studied interventions were steroids (4,141 patients), vitamin D (3,652 patients), and vitamin D + steroids (3,801 patients). In all, 38 of the 100 randomized comparisons were between a topical intervention and an inactive control, and 29 were between steroids and other topical interventions. The comparisons between steroids and vitamin D and those between vitamin D, steroids, or vitamin D + steroids and an inactive control were the most represented, without significant co-occurrence (*C*-score 13.3, $P = 0.53$). Among the 19 RCTs registered in ClinicalTrials.gov, 6 (32%) were two-arm trials against an inactive control (Figure 1b). The most-studied interventions were experimental topical drugs. In all, 20 of the 41 (50%) randomized comparisons were between a topical intervention and an inactive control, and 50% were between topical drugs.

Trials on CLEWs. The 50 reports of RCTs on CLEWs described 44 different topical drugs that we classified into 15 therapeutic classes (Supplementary File S3 online). The network of trials had considerable diversity (PIE = 0.86). The most-studied interventions were nonsteroid anti-inflammatory drugs and silver. In all, 41 reports (82%) described at least one inactive control arm: in 34 (68%), the intervention was compared against this inactive control only. The network was star-shaped, and comparisons against an inactive control were overrepresented but not significantly (*C*-score 11.2, $P = 0.20$) (Figure 2a). Among the seven trials registered in ClinicalTrials.gov, five involved a control arm with an inactive control, which was the only comparator in four cases (Figure 2b).

Table 1. Characteristics of reports of randomized controlled trials (RCTs) of three dermatologic conditions published from 2007 to 2012

Characteristics of trials	Psoriasis; *n* = 60	Chronic lower-extremity wounds; *n* = 50	Acne vulgaris; *n* = 90
Sample size: median (inter-quartile range)	60 (35–217)	59 (40–121)	87 (53–174)
Geographic area			
North America	18 (30%)	9 (18%)	36 (40%)
South America	1	4 (8%)	2 (2%)
Asia	19 (32%)	6 (12%)	36 (40%)
Europa	22 (37%)	28 (56%)	16 (18%)
Oceania	0	2 (4%)	0
Africa	0	1	0
Multicentric trial	28 (47%)	30 (60%)	47 (52%)
Design of the trial			
Parallel	47 (78%)	50 (100%)	79 (88%)
Split body	13 (22%)	0	11 (12%)
Multi-arm (>2) trials	16 (27%)	7 (14%)	22 (24%)
Comparison involving a combination of topical drugs in at least one arm	17 (28%)	3 (6%)	35 (39%)

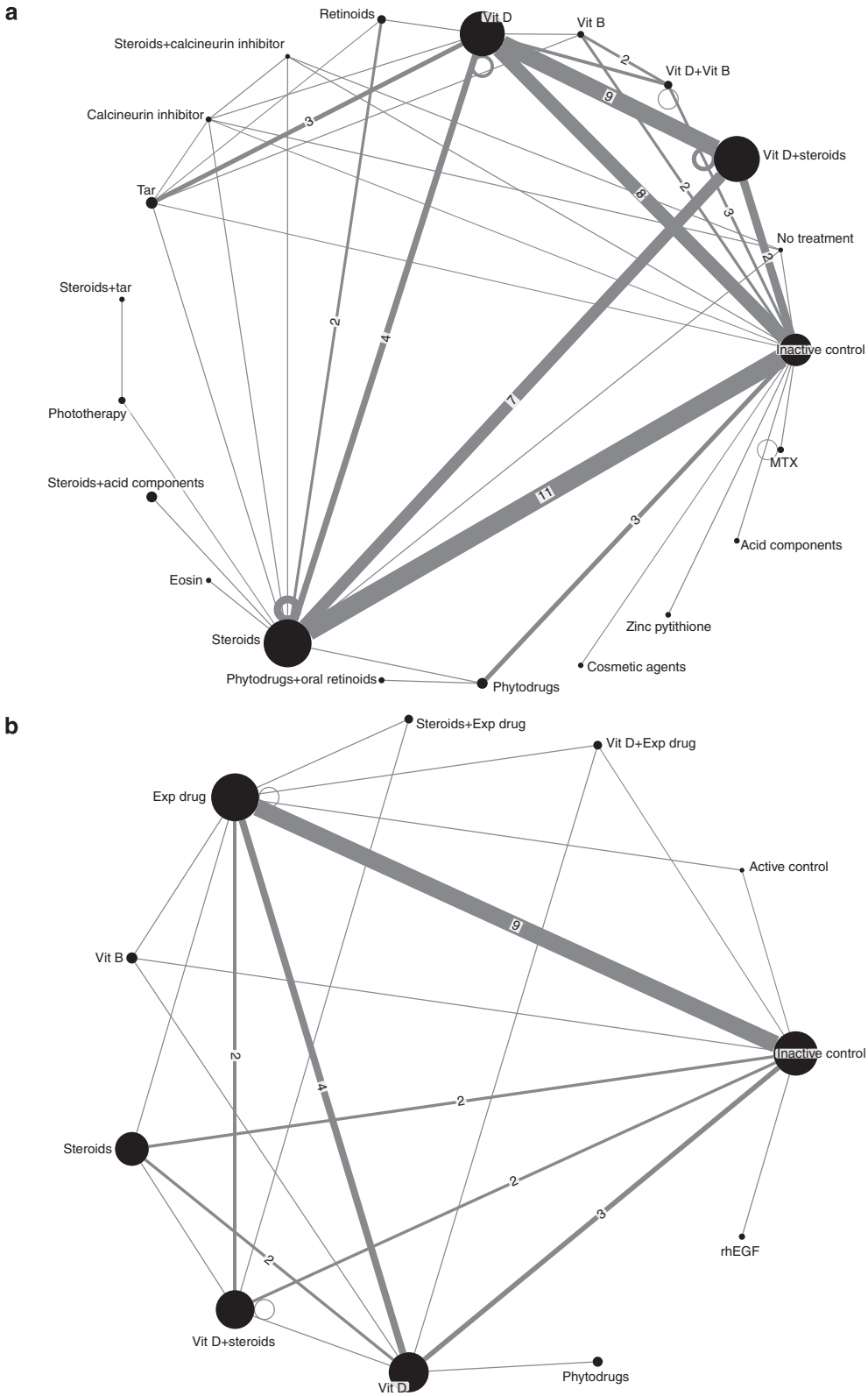

Figure 1. Psoriasis—60 published trials; 19 registered trials. Networks of drugs assessed for psoriasis in reports of randomized controlled trials (RCTs) (**a**) and trials registered in ClinicalTrials.gov (**b**). Nodes represent the interventions—two nodes are linked together by a line (edge) if at least one trial compared the two corresponding interventions. The size of a node is proportional to the total number of patients randomly allocated. The thickness of an edge is proportional to the number of randomized comparisons between the two corresponding interventions. Loops (connecting a node to itself) represent intra-drug comparisons (e.g., doses). Drugs were applied topically unless indicated as oral. MTX, methorexate; Vit, vitamin; rhEGF, recombinant human epidermal growth factor; Exp, experimental (new drugs from a non-specified class).

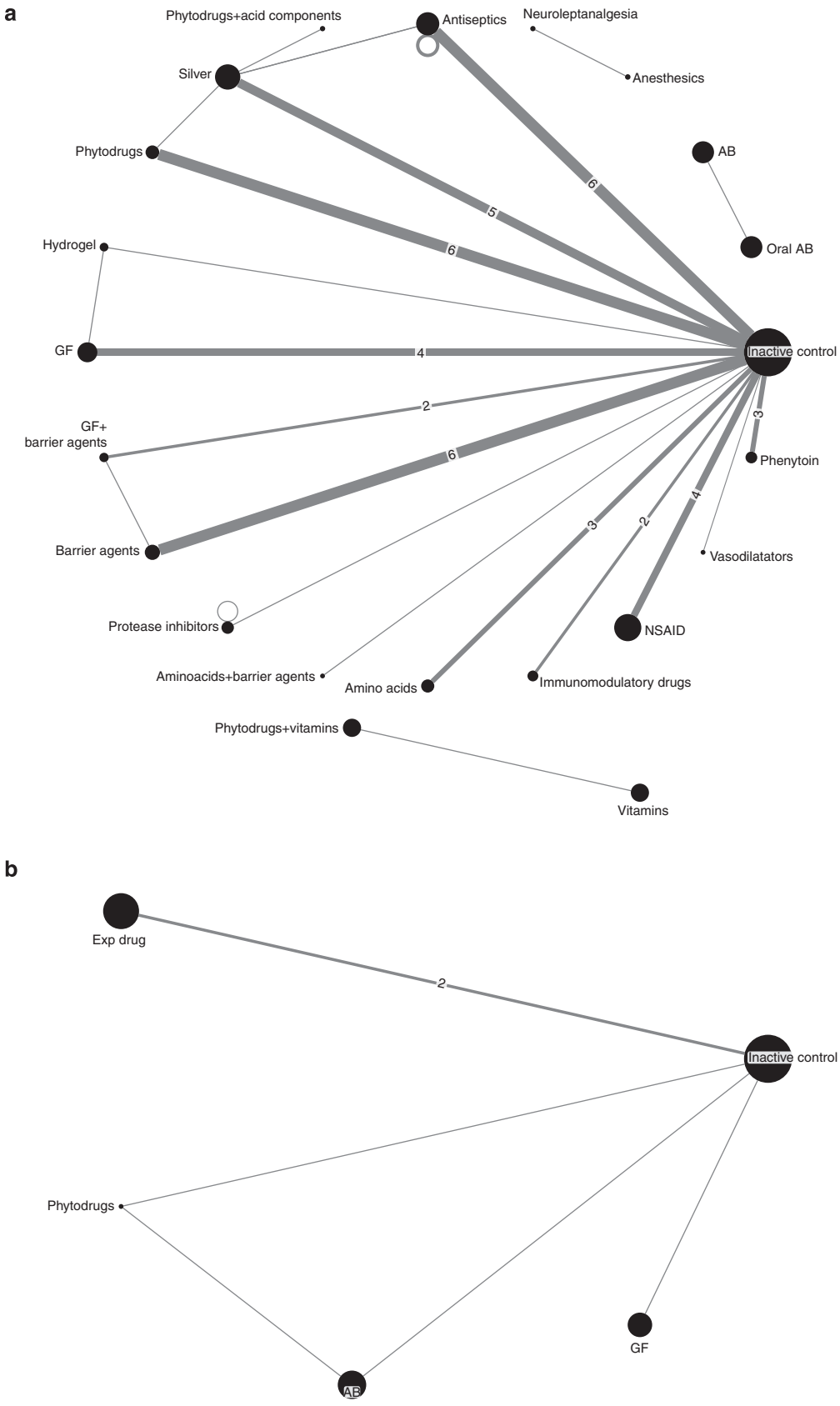

Figure 2. Chronic lower-extremity wounds—50 published trials; 7 registered trials. Networks of drugs assessed for chronic lower-extremity wounds (CLEWs) in reports of randomized controlled trials (RCTs) (**a**) and trials registered in ClinicalTrials.gov (**b**). AB, antibiotics; Exp, experimental; GF, growth factors; NSAID, nonsteroid anti-inflammatory drugs.

Trials on AV. The 90 reports of RCTs on AV described 39 different topical drugs that we classified into 14 therapeutic classes (Supplementary File S3 online). The network of trials had considerable diversity (PIE = 0.89). In all, 51 reports (57%) described active comparators, with a systemic control arm in two cases, and 51 (57%) described at least one inactive control arm: 39 (43%) described comparing the intervention against this inactive control. The most represented comparisons were between topical antibiotics, benzoyl peroxide, or retinoids and an inactive control, without significant co-occurrence (*C*-score 19.0; $P = 0.57$) (Figure 3a). Among the 21 RCTs registered in ClinicalTrials.gov, 15 involved a control arm with an inactive control, which was the only comparator in five cases (Figure 3b).

DISCUSSION

We studied the network of evidence from RCTs on topical drugs for psoriasis, CLEWs, and AV. Reports of RCTs were more numerous for AV than for the other conditions (90 versus 50 and 60, respectively), and studies included a larger number of patients. This finding can be explained by the high frequency of AV in the population (Ghodsi *et al.*, 2009). All networks showed substantial diversity, which is explained by the variety of topical drugs available for these conditions and assessed in RCTs. Indeed for CLEWs, we identified 15 therapeutic classes for 50 trials. Clinical research on this prevalent and painful condition may be constantly driven by the successive topical and even systemic treatments showing disappointing results. CLEWs remain a medical problem of high priority.

Trials that randomize patients to alternative treatments, each with the potential to be the best practice, are fundamental to CER. In our study, comparisons with inactive controls were frequent, especially for CLEWs. In published RCTs, two-arm trials with an inactive control arm represented 22% of reports on psoriasis RCTs, 68% of CLEWs, and 43% of AV RCTs. Although we lack a standard to establish whether a percentage of trials with an inactive control is adequate or not, considering that more than one-third is inadequately high seems relevant. In RCTs of psoriasis, a previous review of publications from 2001 to 2005 showed a high rate of use of placebo (38.5% of trials, corresponding to 58.3% of subjects), but topical and systemic treatments were not analyzed separately (Katz *et al.*, 2006).

Calculations of *C*-scores, reflecting degrees of co-occurrence of interventions assessed, were not statistically significant for the three studied conditions, i.e, we found no head-to-head comparisons that were specifically preferred or avoided. Therefore, our results do not suggest a substantial lack of head-to-head evidence for mild psoriasis and AV, but for CLEWs results are more questionable. Although we demonstrated no significant avoidance of comparisons in trials on CLEWs, inactive controls were highly represented. Also, as clinicians, we noted only a few comparisons of drugs with a close mode of action, such as antiseptics and nonsteroid anti-inflammatory drugs, antibiotics and silver, or protease inhibitors and growth factors.

In other conditions, the lack of head-to-head trials was more evident (Kim *et al.*, in press; Rizos *et al.*, 2011; Kappagoda and Ioannidis, 2012; Estellat and Ravaud, 2012; Tonelli *et al.*, 2013; Ioannidis *et al.*, 2013). For instance, in arthritis, researchers have shown greater lack of head-to-head trials on arthritis psoriasis than we observed for cutaneous psoriasis treated with topical drugs, although arthritis psoriasis is a condition of high functional severity (Estellat and Ravaud, 2012; Ioannidis *et al.*, 2013).

When comparing published RCTs with registered trials not yet published, the proportions of head-to-head trials were similar. Thus, the inactive control remains the preferred comparator, although ethical problems linked to the choice of an inactive comparator has been highlighted, despite the CER initiative (Hochman and McCormick, 2010). The use of inactive control could be preferred because of compliance with regulatory recommendations to ensure that treatment effects are well documented, because of the low cost of using a placebo, and because of trials of inactive comparators more likely than those of active comparators to report positive results (Hochman and McCormick, 2010).

The inactive controls used consisted of topical vehicles or emollients. Although we found high representation of comparisons with inactive controls, these may not be true placebos because they are not totally inactive despite their lack of active principle (Shamsudin and Fleischer, 2010). Indeed, applying excipients on the skin induces physiochemical modifications of the skin barrier, which were demonstrated with transepidermal water loss (Hon *et al.*, 2013). We found the use of inactive controls particularly frequent in studies on CLEWs. Similarly, dressings without the active principle, always used as inactive control in CLEWs trials, may not be true placebos.

Our analysis has some limitations. The most important one was that the search was limited to articles published over 5 years, and the best time to search for the deliberate avoidance of key comparisons is probably when new drugs are introduced. Therefore, studying older reports of RCTs may reveal increased diversity or co-occurrence. However, we aimed to cover a time window around when the CER initiative was launched, in 2009 (Clancy, 2012). Second, our network of published evidence may have been affected by reporting bias. Third, we focused the study on topical drugs, although systemic drugs may also be given in moderate conditions and are more expensive in many cases. The reason for this restriction was to increase homogeneity of the studied population and avoid disjointed networks of trials. Fourth, we did not assess the sponsorship of the study; studies with industry sponsorship are more likely to use inactive comparators for several conditions (Katz *et al.*, 2006; Bourgeois *et al.*, 2012; Dunn *et al.*, 2012; Stamatakis *et al.*, 2013). However, 87% of our selected trials registered in ClinicalTrials.gov had industry sponsorship. Moreover, our study did not allow for assessing the avoidance of comparisons of manufactured combinations of drugs and the active components separately. This analysis would have been interesting because the latter drugs are less costly (Williams *et al.*, 2012). Finally, we included all RCTs regardless of outcomes and follow-up duration. The nature of the networks may evolve depending on the outcome of interest (e.g., efficacy or safety) and according to treatment duration (e.g., short-term or long-term treatment).

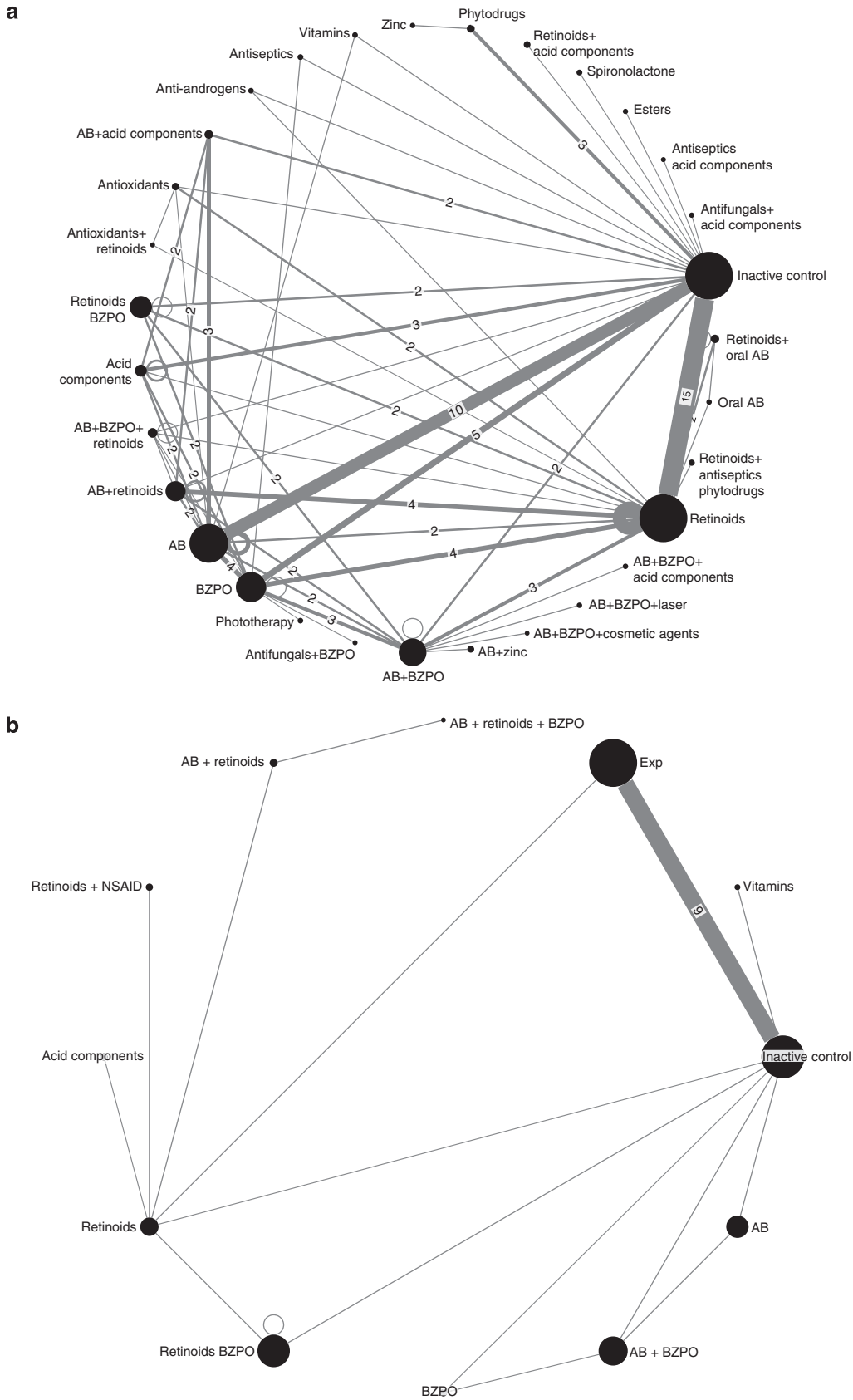

Figure 3. Acne vulgaris—90 published trials; 21 registered trials. Networks of drugs assessed for acne vulgaris in reports of randomized controlled trials (RCTs) (**a**) and trials registered in ClinicalTrials.gov (**b**). AB, antibiotics; BZPO, benzoyl peroxide; NSAID, nonsteroid anti-inflammatory drugs; Exp, experimental.

In conclusion, for three dermatologic topics (psoriasis, CLEWs, and AV) on mild-to-moderate severity with respect to topical treatments, our network analysis of RCTs with published results and ongoing RCTs did not find a significant preference or avoidance of specific comparisons. However, it showed that comparisons with inactive controls were more frequent than were head-to-head trials, especially for CLEWs, for which more comparative effectiveness trials are needed.

MATERIALS AND METHODS

We systematically searched for RCTs that assessed topical drugs in psoriasis, CLEWs, and AV, with results published during a recent 5-year period (from 1 January 2007 to 28 July 2012) or registered in ClinicalTrials.gov (from 1 January 2011 to 28 July 2012).

Selection criteria

We considered RCTs that assessed any topical treatment of three conditions: cutaneous psoriasis, CLEWs, or AV. Cutaneous psoriasis included plaque, guttate, or pustular psoriasis and body, scalp, palmo-plantar, or ungueal topography. CLEWs included arterial, diabetic, and vasculitic leg ulcers. We included trials on AV but not closely related conditions (e.g., acne rosacea). Eligible trials compared in at least one arm a topical treatment with any active or inactive comparator, regardless of RCT design and outcomes. Multi-dose trials were eligible. We focused on topical drugs because of the following reasons: (1) they are the first-line treatment for the studied dermatologic conditions; (2) they constitute a great amount of prescriptions and represent a major cost to the public; (3) apart from the cost, a very large population is exposed to topical drugs; and (4) we could restrict the study to a homogeneous group of patients (e.g., with mild to moderately severe conditions).

We excluded non-randomized trials, trials on healthy volunteers, and interventional trials of treatments other than drugs; in particular, we excluded trials of devices, which are numerous in CLEWs, because we focused on active topical drugs often incorporated in dressings. We excluded RCTs with results published as abstracts only. With two publications for one RCT, we included the most recent publication.

Search strategy

We searched for systematic reviews in the Cochrane Library and screened lists of trials included in relevant reviews. We also searched for reports of RCTs in the Cochrane Central Register of Controlled Trials, in MEDLINE, and in EMBASE. The searches covered the period from 1 January 2007 to 28 July 2012. Search equations created by an information specialist (GF) were designed for each condition and each database (see Supplementary File S2 online). We also searched ClinicalTrials.gov for RCTs registered from 1 January 2011 to 28 July 2012. We chose to consider RCTs registered after 2011 to avoid double counting published trials.

Data extraction and categorization of interventions

Selection of trials was performed by one author (AM). For each selected trial, we extracted information on the first author, publication year, journal, country/site, trial design (parallel arm, cross-over, or split body) and number of arms, interventions and comparators, as well as the number of patients randomly allocated to each arm. Two authors, who are dermatologists (AM, LLC), independently and in duplicate classified topical drugs into therapeutic classes (Yu and Van Scott, 2004, see Supplementary File S3 online). We defined an inactive control as a topical intervention without the active principle (vehicle or placebo). Discrepancies in classifying drugs were resolved with a third dermatologist (GL).

Trial networks

For each condition, we produced networks of RCTs with published results and registered trials. When a multi-arm trial compared two interventions belonging to the same therapeutic class (e.g., with different dosages), we considered the two as one intervention (and we added the number of patients). We produced network graphs in which nodes (or vertices) represented the interventions, and lines linking nodes (edges) indicated that at least one RCT compared the two interventions linked. The size of a node was proportional to the total number of patients randomly allocated to the corresponding intervention. The thickness of an edge was proportional to the number of randomized comparisons between the two corresponding interventions. Loops (connecting a node to itself) represent intra-drug comparisons (e.g., comparisons of the same drug at different doses).

We assessed the network geometry: how many head-to-head comparisons between interventions were assessed by at least one trial and how many randomized comparisons were against an inactive control. We assessed the network diversity, which increases with the number of interventions in the network and for a given number of interventions and decreases when the interventions are not equally represented (Salanti *et al.*, 2008). We calculated the PIE: values $\leqslant 0.75$ are considered to reflect limited diversity (Hurlbert, 1971).We also assessed the degree of co-occurrence, which increases when particular head-to-head comparisons of specific interventions are preferred or avoided (Stone and Roberts, 1990). We used the *C*-score statistic for co-occurrence (larger values correspond to a larger degree of co-occurrence) and reported the associated *P*-values (Salanti *et al.*, 2008).

Analyses involved the NodeXL add-in for Excel 2007 (Social Media Research Foundation), R v3.0.2 (R Development Core Team, Vienna, Austria), and EcoSim v7 (http://www.uvm.edu/~ngotelli/EcoSim/EcoSim.html).

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank Gaëlle Fanelli, information specialist, for her documentation help. The study was supported by the Association Recommandations En Dermatologie (aRED, committee of the French Society of Dermatology).

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

REFERENCES

Bourgeois FT, Murthy S, Mandl KD (2012) Comparative effectiveness research: an empirical study of trials registered in ClinicalTrials.gov. *PLoS ONE* 7:e28820

Clancy CM (2012) A push for comparative effectiveness: US initiatives aim to empower patients, physicians. Interview by Bridget M. Kuehn. *JAMA* 307:1570–1

Dunn AG, Bourgeois FT, Murthy S *et al.* (2012) The role and impact of research agendas on the comparative-effectiveness research among antihyperlipidemics. *Clin Pharmacol Ther* 91:685–91

Estellat C, Ravaud P (2012) Lack of head-to-head trials and fair control arms. *Arch Intern Med* 172:237–44

Ghodsi SZ, Orawa H, Zouboulis CC (2009) Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *J Invest Dermatol* 129:2136–41

Hochman M, McCormick D (2010) Characteristics of published comparative effectiveness studies of medications. *JAMA* 303:951–8

Hon KL, Pong NH, Wang SS *et al.* (2013) Acceptability and efficacy of an emollient containing ceramide-precursor lipids and moisturizing factors for atopic dermatitis in pediatric patients. *Drugs R D* 3:37–42

Hurlbert SH (1971) The nonconcept of species diversity: a critique and alternative parameters. *Ecology* 52:577

IOM (Institute of Medicine) (2009) Initial National Priorities for Comparative Effectiveness Research. The National Academies Press: Washington, DC

Ioannidis JP, Karassa FB (2010) The need to consider the wider agenda in systematic reviews and meta-analyses: breadth, timing, and depth of the evidence. *BMJ* 341:c4875

Ioannidis JP, Karassa FB, Druyts E *et al.* (2013) Biologic agents in rheumatology: unmet issues after 200 trials and $200 billion sales. *Nat Rev Rheumatol* 9:665–73

Kappagoda S, Ioannidis JPA (2012) Neglected tropical diseases: survey and geometry of randomised evidence. *BMJ* 345:e6512

Katz KA, Karlawish JH, Chiang DS *et al.* (2006) Prevalence and factors associated with use of placebo control groups in randomized controlled trials in psoriasis: a cross-sectional study. *J Am Acad Dermatol* 55:814–22

Kim DD, Tang JY, Ioannidis JP (2014) Network geometry shows evidence sequestration for medical vs. surgical practices: treatments for basal cell carcinoma. *J Clin Epidemiol* 67:391–400

Kivelevitch DN, Hebeler KR, Patel M *et al.* (2013) Emerging topical treatments for psoriasis. *Expert Opin Emerg Drugs* 18:523–32

Lapolla WJ, Levender MM, Davis SA *et al.* (2011) Topical antibiotic trends from 1993 to 2007: use of topical antibiotics for non-evidence-based indications. *Dermatol Surg* 37:1427–33

Melnikova I (2009) Psoriasis market. *Nat Rev Drug Discov* 8:767–8

Mills EJ, Thorlund K, Ioannidis JP (2013) Demystifying trial networks and network meta-analysis. *BMJ* 346:f2914

Nambudiri VE, Qureshi A (2013) Comparative effectiveness research. *J Invest Dermatol* 133:e5

Rizos EC, Salanti G, Kontoyiannis DP *et al.* (2011) Homophily and co-occurrence patterns shape randomized trials agenda: illustration in antifungal agents. *J Clin Epidemiol* 64:830–42

Salanti G, Higgins JP, Ades AE *et al.* (2008) Evaluation of networks of randomized trials. *Stat Methods Med Res* 17:279–301

Salanti G, Kavvoura FK, Ioannidis JP (2008) Exploring the geometry of treatment networks. *Ann Intern Med* 148:544–53

Seité S, Rougier A, Dréno B (2012) Enquête sur la prise en charge des patients acnéiques en France. *Ann Dermatol Venereol* 139:611–6

Shamsudin N, Fleischer AB Jr (2010) Vehicle or placebo? Investigators use incorrect terminology in randomized controlled trials half of the time: a systematic review of randomized controlled trials published in three major dermatology journals. *J Drugs Dermatol* 9:1221–6

Sox HC, Greenfield S (2009) Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med* 151:203–5

Stamatakis E, Weiler R, Ioannidis JP (2013) Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review. *Eur J Clin Invest* 43:469–75

Stone L, Roberts A (1990) The checkerboard score and species distributions. *Ecologia* 85:74–9

Tonelli AR, Zein J, Ioannidis JP (2013) Geometry of the randomized evidence for treatments of pulmonary hypertension. *Cardiovasc Ther* 31:e138–46

Wan J, Abuabara K, Troxel AB *et al.* (2012) Dermatologist preferences for treatments to compare in future randomized controlled comparative effectiveness trials for moderate to severe psoriasis. *Arch Dermatol* 148:539–41

Williams HC, Dellavalle RP, Garner S (2012) Acne vulgaris. *Lancet* 379: 361–72

Yu RJ, Van Scott EJ (2004) Alpha-hydroxyacids and carboxylic acids. *J Cosmet Dermatol* 3:76–87

Zenilman J, Valle MF, Malas MB *et al.* (2013) *Chronic venous ulcers: a comparative effectiveness review of treatment modalities*. Agency for Healthcare Research and Quality (US): Rockville, MD