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Most randomized controlled trials for psoriasis used placebo comparators despite the availability of effective treatments

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## **ABSTRACT**

**Background:** The availability of effective treatments for psoriasis raises ethical questions about the use of a placebo group in therapeutic trials. We evaluated the use of the placebo over time in such trials.

**Methods:** From trials in a living Cochrane review and network meta-analysis (NMA) for psoriasis, we included trials comparing a biologic to a placebo or other systemic treatment. First, we tested the changes in placebo rate from 2001 to 2019 by linear regression, then constructed networks for 2004-2019 and evaluated the contribution of the placebo to the NMA estimates per trial and per comparison.

**Results:** We included 81 trials (36,774 patients). The placebo rate did not decrease significantly over time. The proportion contribution of trials with a placebo decreased from 100% in 2004 to 86% in 2008 and 75% in 2019. However, the proportion contribution of trials without a placebo remained low (from 0% in 2004 to 25% in 2019).

**Conclusion:** The design of future psoriasis trials should be reviewed to improve the number of patients to be included in a placebo group.

**Keywords:** Placebo, Clinical Trials, Psoriasis, Ethics

**Words:** 175

**Running title:** placebo use in randomized controlled trials for psoriasis

**What is new ?**

- Despite the increasing availability of effective molecules, the use of the placebo group in therapeutics trials for psoriasis has not decreased over time.
- Thus, depriving patients in the placebo group of effective and approved treatments may expose them to serious harm, such as worsening their psoriasis.
- Future psoriasis trial design needs to be reviewed to better assess the number of patients to be included in the placebo group for a new molecule.

## 1. INTRODUCTION

In trials of drugs, the placebo is an inactive substance that looks the same as and is given in the same way as an active drug being studied [1]. The use of a placebo as a comparator in a randomized controlled trial (RCT) is ethically justified under the following conditions: 1) no proven effective intervention, 2) no or negligible harms from delaying or forgoing treatment, 3) when evaluating a disease associated with a variable or fluctuating response to placebo and treatment, and 4) if for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo will not be subject to any risk of serious or irreversible harm according to the Declaration of Helsinki of 2013 [2–4]. Thus, placebo-controlled trials raise ethical issues when a proven effective treatment exists, as in several inflammatory diseases including psoriasis, and seems to conflict with the equipoise principle [5–10]. This principle is a fundamental rule in the conduct of RCTs and states that patients should only be enrolled in an RCT if there is significant uncertainty about the most appropriate investigational treatment for them [11, 12].

Psoriasis is a common chronic immune-mediated inflammatory skin disease that affects 2% to 3% of the world's population [13, 14]. There are effective treatments that can lead to remissions or an improvement phase. The most recent living Cochrane systematic review and NMA, combining direct and indirect evidence of RCTs, compared the efficacy of 19 systemic treatments in psoriasis and found that 69% of the comparisons involved a placebo group [15, 16].

The increase in number of available treatments and their effectiveness for psoriasis may have led to a change of RCT design, with reduced use of the placebo group over time. This study

aimed to 1) assess the placebo rate over time, and 2) estimate the contribution of the placebo group to NMA estimates per RCT and per comparison.

## **2. MATERIALS AND METHODS**

### **2.1. Criteria for considering studies for this review**

We included all RCTs from the most recent version of a living Cochrane review and NMA and excluded those comparing two doses or two modes of administration of the same molecule in the absence of the placebo group or other active comparator. We considered RCTs that included adults (> 18 years old) with moderate to severe plaque psoriasis and assessed biologic treatments, regardless of the dose and duration of treatment, compared with placebo and/or biologic treatment and/or other systemic treatment. Experimental treatments included anti-tumor necrosis factor (TNF)- $\alpha$  (infliximab, etanercept, adalimumab, certolizumab), anti-interleukin 12/23 (IL-12/23) (ustekinumab), anti-IL-17 (secukinumab, brodalumab, ixekizumab, bimekizumab) and anti-IL-23 (tildrakizumab, guselkumab, risankizumab). For multi-dose trials, we included all doses and merged them.

We used data from RCTs included in the last version of the living Cochrane review and NMA of chronic plaque psoriasis with a final research update in May 2020 [15].

### **2.2. Outcomes**

First, we assessed the placebo rate in a given year (i.e., proportion of randomized patients in the placebo group). Second, we estimated the contribution matrix of the placebo group per RCT and per comparison in NMA estimates over time. The contribution matrix shows “how much information (expressed as a percentage) each study or each comparison contributes to

the results from NMA” [17]. This methodology is used in evaluating confidence in the findings from NMA.

### **2.3. Data selection and extraction**

One reviewer (SA) selected reports on the basis of the title and abstract and then the full text according to previously established inclusion criteria. The following data were extracted from reports by one reviewer (SA) using a standard data extraction form: 1) the patient characteristics at baseline (i.e., age, sex, Psoriasis Area and Severity Index 75, comorbidities such as psoriatic arthritis) and 2) RCT characteristics (i.e., year of publication, total number of randomized patients, number of randomized patients in each group, ratio of randomisation, location (Europe, Asia, USA, worldwide (more than 2 continents)), number of arms, and treatments [for RCTs assessing 2 different treatments, treatments were retained as interventions for the new treatment and not the comparator], therapeutic class (anti-TNF- $\alpha$ , anti-IL-17, anti-IL-23, anti-IL-12/23), placebo group vs experimental treatment (yes/no), experimental treatment vs active molecule (yes/no), experimental treatment vs active molecule vs placebo [yes/no], first molecule into its therapeutic class (yes/no)).

### **2.4. Classification of trials**

Each RCT was classified according to 1) the presence or absence of a placebo group and 2) the equipoise principle for which the allocation randomization is equal (e.g., = 1:1 with two arms) [11]. Thus, RCTs were divided into three groups: 1) no placebo group, 2) placebo with randomization ratio < 1:1 and 3) placebo with randomization ratio = 1:1.

## **2.5. Statistical analyses**

### **2.5.1. Descriptive analysis**

We summarized the main characteristics of the study population and RCTs by mean  $\pm$  standard deviation (SD) or median with interquartile range (IQR<sub>25-75</sub>) for quantitative variables and number (percentage) for qualitative variables.

### **2.5.2. Analytical analysis**

We used two different methods to assess the use of the placebo group in therapeutic RCTs for psoriasis over time.

#### *Interrupted time series analysis*

First, we used a segmented linear regression model to determine the impact of increasing therapeutic options on change over time in placebo rate. Four highly effective biologic treatments among 12 were marketed in 2014. The dates of US Food and Drug Administration (FDA)-approved biologic treatments for psoriasis are summarized in Additional file 1 : Table S1. We considered a pre-period (from 2000 to 2014) and post-period (from 2015 to 2019). The results are expressed as an estimate coefficient  $\pm$  standard error (SE) and its 95% confidence interval (CI). The dependent variable was the placebo rate (i.e., proportion of randomized patients in the placebo group). The independent variable was the year of publication. No seasonal variation was expected. Stationarity was assessed with the augmented Dickey–Fuller and Phillips–Perron tests. The assumptions for autocorrelation and linear regression were met [18, 19]. With no change in level ( $\beta_2$ ) or no change in trend between the pre and the post-periods, the most parsimonious model would be generated in a simple linear regression (i.e., a model with an estimation of the trend all over the study period). A post-hoc sensitivity analysis was performed with a 2-year period (2001-2018) as

the independent variable to take into account 1) the year 2009 when no patients were included in a placebo group and 2) the year 2002 when no RCTs were published.

### Contribution of placebo group to the NMA estimates over time

Second, we constructed network graphs of RCTs per year, starting from the year when the first molecule in psoriasis was approved by the FDA. We assessed the contribution of the placebo group in each network. The contribution matrix shows “the contribution of information (expressed as a percentage) of each study or each comparison to the estimation of each relative treatment effect from NMA” [17]. The relative treatment effect of NMA is calculated by combining the available direct evidence of the relative treatment effect (i.e., the results from pairwise meta-analyses) with the indirect evidence on the treatment effect, called mixed evidence [16]. To obtain the contribution matrices, we estimated the direct evidence by using a random-effects pair meta-analysis. The contribution matrix of the placebo group was calculated at the study level (i.e., the contribution of RCTs with a placebo group of randomization ratio < 1:1, a placebo group of randomization ratio = 1:1, and no placebo group) and then at a comparison level.

All tests were two-tailed, and the threshold for statistical significance was set to  $P < 0.05$ . All statistical analyses were performed with Stata v16.0 (StataCorp, College Station, TX) and by using the Confidence in Network Meta-Analysis (CINeMA) web application for the contribution matrices [20, 21].

## **3. RESULTS**

### **3.1. Trial flow and study characteristics**



Among the 140 RCTs included in the Cochrane review, 59 were excluded because they did not meet the inclusion criteria. The reasons for the exclusion of RCTs are available in Additional file 4: Figure S1. The remaining 81 RCTs involving 36,774 patients were included in our analysis (Table 1). Forty-four RCTs out of 81 (54%) were international multicentre trials conducted in more than 2 continents: 50 (62%) had a placebo group as the only comparator; 14 (17%) included a placebo and active treatment as comparators; and 17 (21%) no placebo group. The proportion of RCTs with only placebo as a comparator was higher for the first approved class (anti-TNF-alpha) than the most recent ones (anti-IL-12/23, then anti-IL-17, then anti-IL-23), whereas that with both placebo and active comparators was higher for the most recent classes (anti-IL-17 and anti-IL-23) than others. The total number of patients included in the placebo group was 7,392 (20%). The characteristics of RCTs and their populations by therapeutic class are in Table 1 and by each treatment in Additional file 2: Table S2. The rate of placebo per RCT is described graphically in Additional file 5: Figure S2.

We used two different methods to assess the use of the placebo group in therapeutic RCTs for psoriasis over time.

### **3.2. Interrupted time series analysis**

Figure 1 described the placebo rate per year. We observed a year-to-year fluctuation, especially in 2009 (no participant in a placebo group) and in 2013 (50% of participants in a placebo group). These fluctuations are related to the number of RCTs used to calculate the placebo rate: from one RCT (in 2009 or 2013) to 10 RCTs in 2018 (Figure S2). Using the segmented linear regression analysis, we obtained one curve in the pre-period and another in the post-period (before and after 2014). We observed no change in level or in trend between

the 2 periods, i.e. the increasing number of therapeutic options over time was not associated with a decrease in placebo use in RCTs (Table 2 and Figure 1). In addition, the final linear regression model did not show a significant change of placebo rate over the study period (coefficient per year  $\pm$  SE =  $-0.007 \pm 0.005$  [95%CI  $-0.020 - 0.004$ ];  $P=0.211$ ; Figure 2 and Table 2). This corresponds to a non-significant decrease of 7 patients per 1,000 patients in the placebo group per year. The post-hoc sensitivity analysis showed similar results in the placebo rate from 2004 to 2018 (coefficient per 2 years  $\pm$  SE =  $-0.020 \pm 0.011$  [95%CI  $-0.048 - 0.007$ ];  $P=0.133$ , Table 2 and Additional file 6: Figure S3).

### **3.3. Contribution of placebo group to the NMA estimates over time**

We built 14 network graphs of RCTs per year between 2004 and 2019 (Figure 2). Additional file 3: Table S3 details the number of RCTs, comparisons, interventions and the contribution of the placebo group to each network. The number of RCTs in each network ranged from 4 in 2004 to 81 in 2019, and the number of comparisons from 2 in 2004 to 35 in 2019. The number of multi-arm RCTs increased over time from 0% in 2004 to 17.5% in 2019.

Of all RCTs that contributed to NMA estimates, most included a placebo group: from 86% in 2008 to 75% in 2019 (Figure 3). Starting in 2012, the contribution to NMA estimates of RCTs with a placebo group and using a randomization ratio =1:1 decreased, whereas RCTs with a placebo group and using a randomization ratio < 1:1 increased (Figure 3). Among all the comparisons contributing to NMA estimates, most included a placebo as a comparator, with a decreased use almost equal to 20% (from 71% in 2008 to 55% in 2019 (Figure 4)).

## **4. DISCUSSION**

Our analysis used two different methods to assess the use of a placebo group over time in RCTs of psoriasis. The first showed that the placebo rate did not significantly decrease over time (i.e. non-significant decrease of 7 patients per 1,000 patients in the placebo group per year between 2001 and 2019). These findings were consistent with those of the contribution matrix method, highlighting that the RCTs still tend to include a placebo group over time. However, the number of multi-arm RCTs increased over time, resulting in a 20% decrease in comparisons using a placebo group that contributed to NMA estimates.

Several arguments may explain the lack of a significant reduction in use of the placebo group. First, according to the FDA's 2001 "Guidance for Industry" document, placebo controls are acceptable in trials designed to demonstrate "efficacy", a standard that must be met to obtain FDA approval for a new drug or biologic treatment [22]. Second, the 2004 guideline on "Clinical Investigation of Drugs Indicated for the Treatment of Psoriasis" published by the European Medicines Agency recommends the use of a placebo group because of the seasonal and fluctuating nature of the disease to determine the sensitivity of the study [23]. Finally, placebo-controlled trials require smaller sample sizes, shorter study duration and lower cost than other trials [6, 24]. Given these requests, an initial phase 3 placebo-controlled trial seems necessary to demonstrate the efficacy of a new molecule and is useful and regulatory, but does not explain why subsequent trials assessing the same molecules use a placebo as a control.

In our study, the contribution to NMA estimates of RCTs with a placebo group and using a randomization ratio =1:1 decreased in favour of RCTs also with a placebo group but using a randomization ratio < 1:1. This unbalanced randomization could call into question clinical equipoise, with results associated with unbalanced RCTs significantly more often positive than those associated with corresponding balanced RCTs [25]. Although unbalanced

randomization is sometimes justified by “the desire to expose fewer patients to potentially inferior treatment (i.e. placebo)” as stated in the FDA's 2001 "Guidance for Industry" document [22, 26], this rationale is fundamentally unethical because an honest null hypothesis does not exist at the beginning of the trial [27]. Often, unbalanced randomization is used to collect more data on safety of the new treatment.

The use of a placebo group in a disease such as psoriasis, for which there are many effective molecules (i.e. more than 80% of patients had a 90% improvement of psoriasis with the most recent biologic treatments), raises the question of ethics [15]. Indeed, it is no longer acceptable to treat a patient with an inferior treatment, such as a placebo. Depriving patients in the placebo group of effective and approved treatments may expose them to a psoriasis worsening severe enough to be considered as a serious adverse event (SAE). Indeed, among patients who reported a SAE (which is defined as any untoward medical event that results in death, is life-threatening, requires hospitalization or prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect), the number of patients with psoriasis worsening was greater in the placebo group than in the treatment group ( $n = 23/117$ , 20% vs.  $n = 17/373$ , 5%) (meta-analysis of 51 RCTs comparing a biologic treatment with placebo) [28, 29]. However, the absolute risk was low : the worsening of psoriasis as a SAE occurred in 13/17006 in the biological group (0.076%) compared to 22/5608 (0.392%) in the placebo group. Head-to-head RCTs are required to determine the real comparative risk/benefit ratios of different treatments [30, 31]. This situation is not specific to psoriasis and has been highlighted in other areas. For example, out of 91 RCTs identified in rheumatoid arthritis using biological disease-modifying antirheumatic drugs (DMARDs), only 5 compared biological DMARDs with each other [7]. Moreover, of the 212 registered trials using anti-TNFs in psoriasis, psoriatic arthritis and ankylosing spondylitis, only 38 (18%) included direct comparisons between biological agents

[32]. This issue was also raised in neuropsychiatric conditions by Dunn et al. 2013, where of the 421 trials included, 11% used an active comparator, while 45% used a placebo and 44% without any comparator [33].

The main limitation of this study is that we might not have reached the statistical power needed to show a significant decrease in the placebo rate. However, the set of RCTs used was obtained from the living Cochrane review of systemic treatments for psoriasis, which was performed on the basis of comprehensive research [15]. The second strength is the use of two different methods to assess the use of the placebo group over time, one for the placebo rate and the other for the contribution of the placebo group to NMA estimates.

## **5. CONCLUSIONS**

This study demonstrates that the placebo rate in psoriasis RCTs did not decrease significantly over time up to 2019 despite the increasing availability of effective molecules. Drug agencies require placebo-only trials to limit the risk of wrongly concluding an effect of the drug. However, this requirement does not explain the majority of RCTs using a placebo group. Future psoriasis RCT designs need to be reconsidered to better assess the number of patients to be included in the placebo group for a new molecule.

## **ABBREVIATIONS**

RCT: randomized controlled trial; NMA: network meta-analysis; IL: interleukin; TNF: tumor necrosis factor; SD: standard deviation; IQR :interquartile range; FDA:Food and Drug Administration; SE: standard error; CI: confidence interval; CINeMA: Confidence in Network Meta-Analysis; PBO: placebo.

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## **AUTHOR'S CONTRIBUTIONS**

Sivem Afach: Formal analysis-Equal, Methodology-Equal, Software-Equal, Writing-original draft-Equal, Writing-review & editing-Equal

Theodoros Evrenoglou: Formal analysis-Equal, Methodology-Equal, Software-Equal, Writing-review & editing-Equal

Nadia Oubaya: Formal analysis-Equal, Methodology-Equal, Software-Equal, Writing-review & editing-Equal

Laurence Le Cleach: Conceptualization-Equal, Formal analysis-Equal, Methodology-Equal, Project administration-Equal, Software-Equal, Supervision-Equal, Writing-original draft-Equal

Emilie Sbidian: Conceptualization-Equal, Data Curation-Equal, Methodology-Equal, Project Administration-Equal, Resources-Equal, Supervision-Equal, Validation-Equal, Writing-original Draft-Equal, Writing-review & Editing-Equal

## **CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

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**Table 1.** Characteristics of the trials included and their population by drug class.

	<b>Biologics</b>	<b>Anti-TNF-<math>\alpha</math></b>	<b>Anti-IL-12/23</b>	<b>Anti-IL-17</b>	<b>Anti-IL-23</b>
<b>Characteristics of RCTs</b>					
<b>Total RCTs, n (%)</b>	81	29 (36)	9 (11)	25 (31)	18 (22)
No PBO group	17 (21)	5 (17)	2 (22)	4 (16)	6 (33)
PBO group only	50 (62)	21 (93)	7 (78)	16 (64)	6 (33)
Active + PBO groups	14 (17)	3 (10)	0	5 (20)	6 (33)
<b>Ratio of randomisation, n (%)</b>					
No PBO	17 (21)	5 (17)	2 (22)	4 (16)	6 (33)
PBO with ratio < 1:1	30 (37)	13 (45)	1 (11)	7 (28)	9 (50)
PBO with ratio =1:1	34 (42)	11 (38)	6 (67)	14 (56)	3 (17)
<b>RCT location, n (%)</b>					
Europe	10 (12)	5 (19)	1 (11)	2 (8)	2 (11)
Asia	13 (16)	6 (22)	3 (33)	2 (8)	2 (11)
America	12 (15)	8 (30)	2 (22)	2 (8)	0

Worldwide	44 (54)	8 (30)	3 (33)	19 (76)	14 (78)
<b>Number of arms, n (%)</b>					
2	30 (37)	15 (52)	3 (33)	5 (20)	7 (39)
≥ 3	51 (63)	14 (48)	6 (67)	20 (80)	11 (61)
<b>Characteristics of patients</b>					
Total patients, n	36774	8879	4015	15270	8610
Patients in PBO group, n (%)	7392 (20)	2261 (25)	1004 (25)	2868 (19)	1259 (15)
Age, mean (SD)	45 (2.5)	45 (2.9)	44.5 (3.3)	44.5 (1.5)	46 (2.5)
Male, n (%)	25420 (69)	5983 (67)	2806 (70)	10574 (69)	6057 (70)
PASI score, mean (SD)	20.5 (3.4)	20 (4.5)	21 (4.4)	20.5 (1.7)	21 (2.4)
Psoriatic arthritis*, n (%)	5381 (22)	1600 (25)	944 (24.5)	1701 (20)	1136 (19)

PBO: placebo; SD: standard deviation; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial.

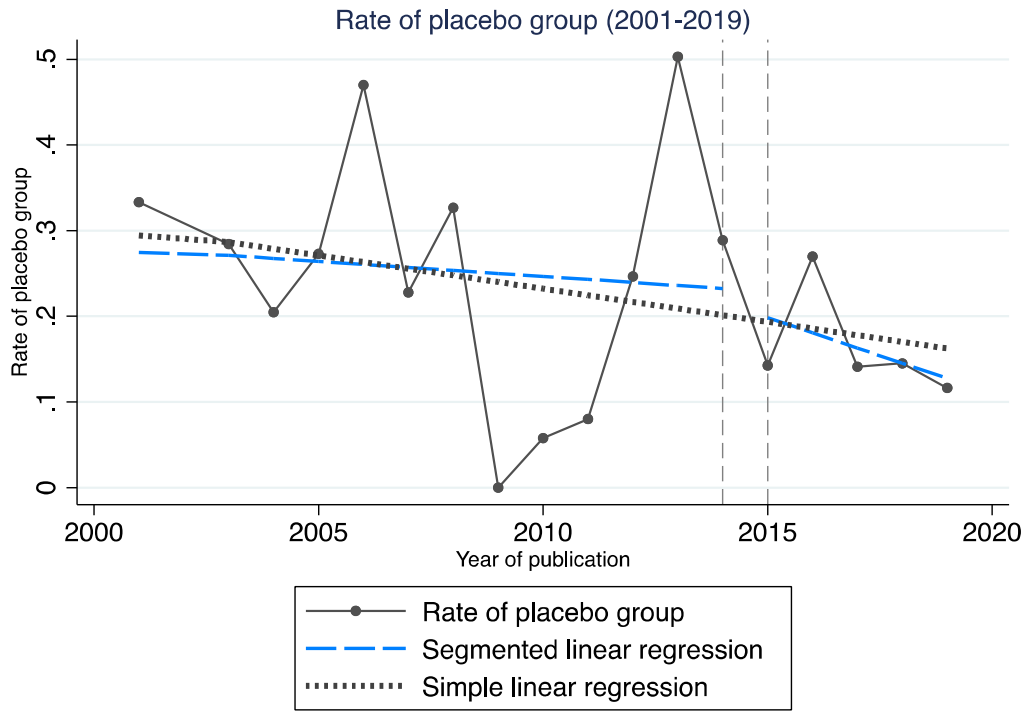
\*51/81 trials in all biologics, 18/29 trials of anti-TNF- $\alpha$ , 8/9 trials of anti-IL-12/23, 13/25 trials of anti-IL-17 and 12/18 trials of anti-IL-23 reported the number of patients with psoriatic arthritis.

**Table 2.** Parameters estimated by the segmented linear regression results.

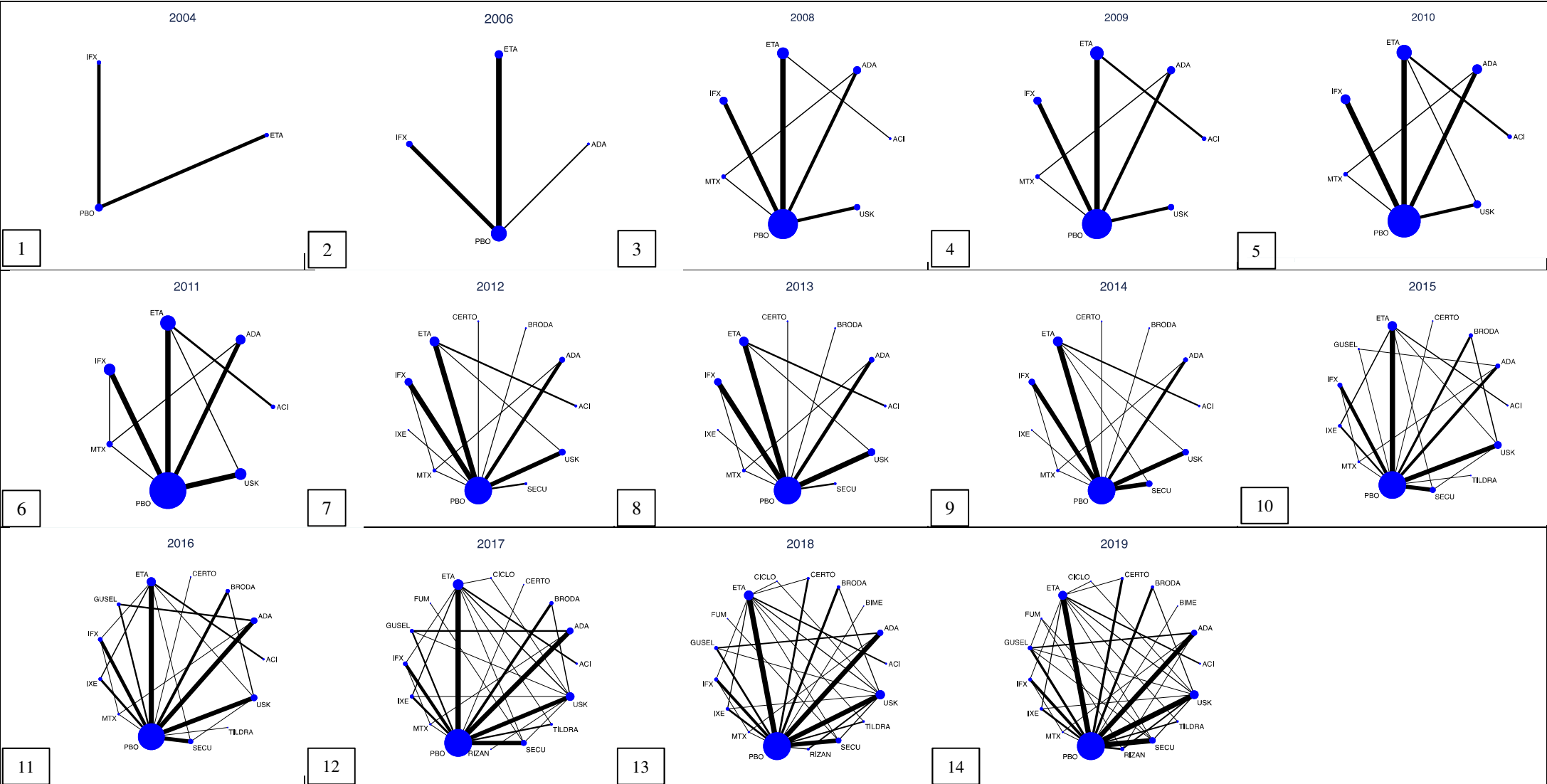
<b>Rate of placebo group</b>	<b>Coefficient</b>	<b>SE</b>	<b>[95% CI]</b>	<b><i>P value</i></b>
<b>Full model: segmented linear regression (2001-2019)</b>				
Baseline level, $\beta_0$	0.278	0.081	0.103 - 0.453	0.004
Baseline trend, $\beta_1$	-0.003	0.010	-0.025 - 0.018	0.738
Change in level after 2014, $\beta_2$	-0.016	0.162	-0.365 - 0.332	0.921
Change in trend after 2014, $\beta_3$	-0.014	0.045	-0.111 - 0.082	0.756
<b>Final model*: simple linear regression (2001-2019)</b>				
Trend	-0.007	0.005	-0.020 - 0.004	0.211
<b>Post-hoc sensitivity analysis: simple linear regression over a 2-year period (2001-2018)</b>				
Trend	-0.020	0.011	-0.048 - 0.007	0.133

\*The final model (i.e., the most parsimonious model).  $\beta_0$ : baseline level for the placebo rate;  $\beta_1$ : baseline trend (i.e., before 2014);  $\beta_2$ : change in level for the placebo rate after 2014;  $\beta_3$ : change in trend after 2014.

SE: standard error; 95% CI: 95% confidence interval.

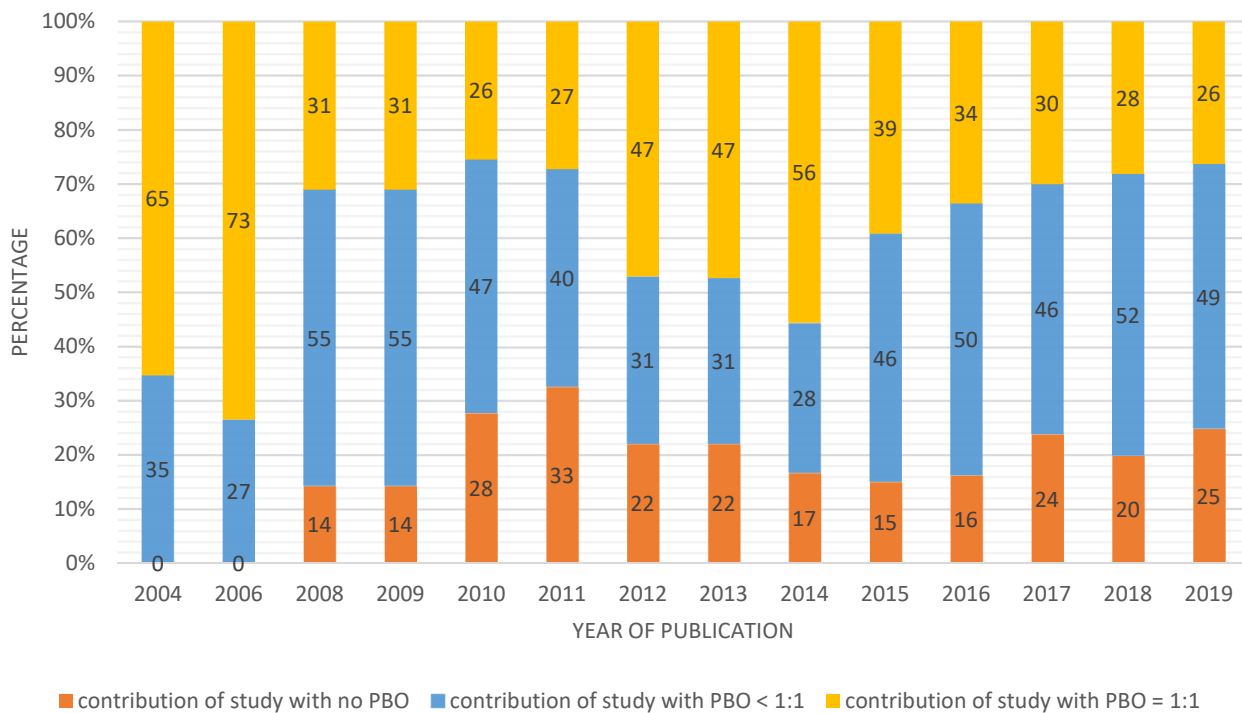


**Figure 1.** Graphical representation of the placebo rate per year (2001-2019).



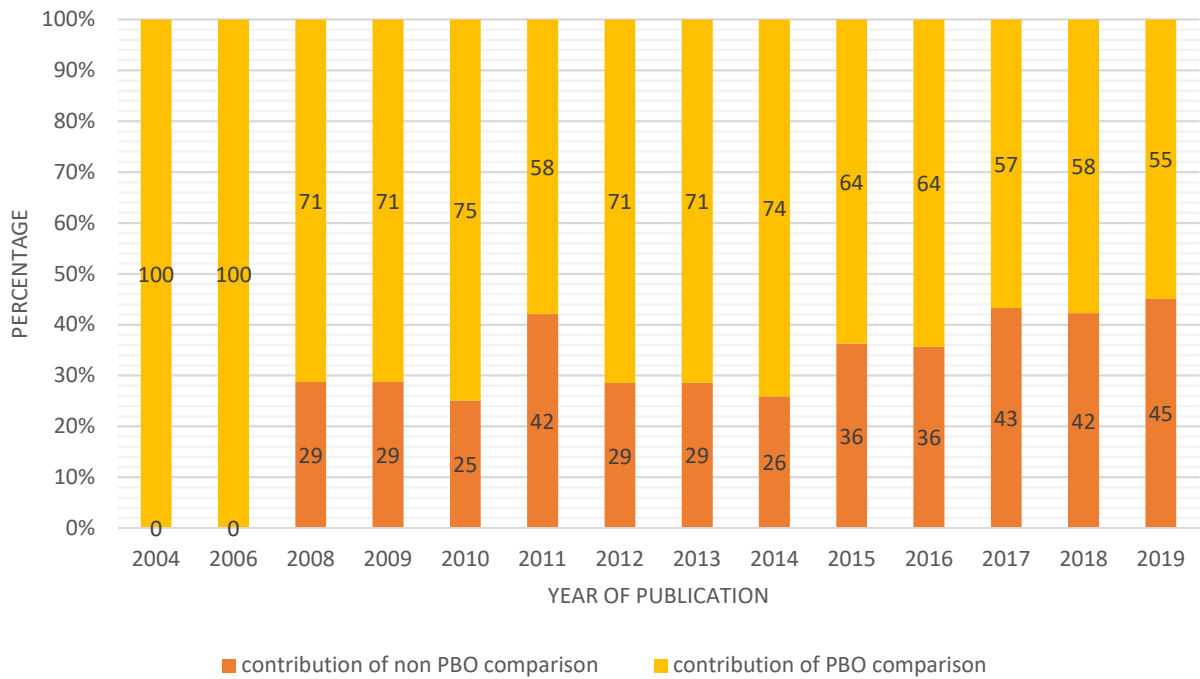
**Figure 2. Network graphs between 2004 and 2019.**

The circle size and line thickness are proportional to the number of studies involved in each direct comparison.  
 ACI= acicretin; ADA=adalimumab; BIME=bimekizumab; BRODA=brodalumab; CERTO=certolizumab; ETA=etanercept; FUM=fumarate; GUSEL=guselkumab; IFX=infliximab;  
 IXE= ixekizumab; PBO= placebo; MTX=methotrexate; RIZAN=rizankizumab; SECU=secukinumab; USK=ustekinumab.



**Figure 3.** Percentage contribution of trials including a placebo group to the network meta-analysis estimates.

PBO: placebo



**Figure 4.** Percentage contribution of comparisons including a placebo group the network meta-analysis estimates.

PBO: placebo