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SAT0434 NETWORK META-ANALYSIS ON THE EFFICACY OF NOVEL THERAPEUTIC AGENTS IN PATIENTS WITH PSORIATIC ARTHRITIS

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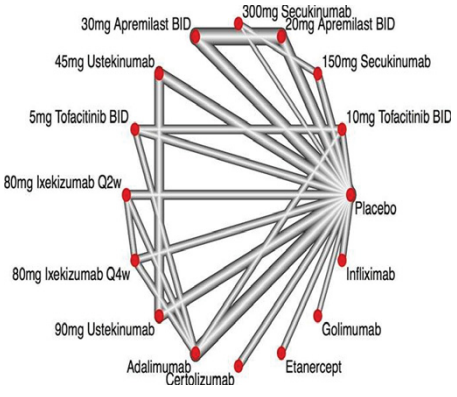
Background: Novel therapeutic agents are more effective than DMARDs in the management of psoriatic arthritis. However, direct comparisons of efficacy between these novel therapeutic agents are lacking.
Objectives: This network meta-analysis aims to compare the relative efficacies between different novel therapeutic agents.
Methods: Literature searching was conducted in MEDLINE, EMBASE, Scopus, ISI Web of Science, Cochrane Library, Clinicaltrials.gov and recent rheumatology conference abstracts up to Nov 2016. 2 independent researchers analysed the articles. For inclusion, randomised, placebo-controlled trials must report the proportion of patients achieving ACR20, ACR50, ACR70 and PASI75 responses. The outcomes of this network meta-analysis were the proportion of patients achieving ACR20, ACR50, ACR70 and PASI75 responses with reference to placebo and etanercept.
Results were analysed using random effect model by R statistics (version 3.3.1) with statistical package netmeta (version 0.9–2). The heterogeneity of the study results was determined by the I^2 statistics.
Results: 18 trials were included into this study. In general, all novel therapeutic agents demonstrated superior efficacies than placebo. With reference to etanercept, apremilast and ustekinumab were associated with less proportions of patients achieving ACR20 response (odds ratio [95% confidence interval]: 20mg apremilast: 0.18 [0.07–0.48]; 30mg apremilast: 0.24 [0.09–0.62]; 45mg ustekinumab: 0.26 [0.09–0.73]; 90mg ustekinumab: 0.32 [0.11–0.90]).
Etanercept was not different from apremilast, ustekinumab, golimumab, adalimumab, ixekizumab, certolizumab, ixekizumab and secukinumab in terms of ACR20 and ACR50 responses.
Golimumab and infliximab were associated with greater proportions of patients achieving PASI75 response, though the difference did not reach statistical significance. (odds ratio [95% confidence interval]: golimumab: 3.51 [0.44–28.2]; infliximab: 5.97 [0.89–40.2]).

Table 1. Network meta-analysis on proportion of patients achieved ACR20 and PASI75 response with reference to etanercept

	ACR20 response	PASI75 response
10mg Tofacitinib BID	0.38 [0.12; 1.22]	0.68 [0.13; 3.54]
150mg Secukinumab	0.64 [0.22; 1.90]	0.49 [0.07; 3.19]
20mg Apremilast BID	0.18 [0.07; 0.49]	0.39 [0.08; 1.83]
300mg Secukinumab	0.77 [0.21; 2.80]	0.67 [0.10; 4.56]
30mg Apremilast BID	0.24 [0.09; 0.63]	0.48 [0.10; 2.22]
45mg Ustekinumab	0.26 [0.09; 0.75]	1.18 [0.15; 9.09]
5mg Tofacitinib BID	0.25 [0.08; 0.81]	0.64 [0.12; 3.29]
80mg Ixekizumab Q2w	0.40 [0.12; 1.27]	2.74 [0.49; 15.37]
80mg Ixekizumab Q4w	0.35 [0.11; 1.11]	1.73 [0.32; 9.31]
90mg Ustekinumab	0.32 [0.11; 0.92]	1.40 [0.18; 10.74]
Adalimumab	0.33 [0.13; 0.86]	0.77 [0.17; 3.50]
Certolizumab	0.42 [0.12; 1.39]	NA
Etanercept (reference)	1.00	1.00
Golimumab	0.93 [0.25; 3.40]	3.51 [0.44; 28.22]
Infliximab	0.74 [0.26; 2.12]	5.97 [0.89; 40.22]
Placebo	0.10 [0.04; 0.22]	0.09 [0.03; 0.35]

NA: not applicable.



Conclusions: Apremilast and ustekinumab were less efficacious than etanercept in terms of ACR20 response. All the novel therapeutic agents demonstrated comparable efficacies in terms of ACR50, ACR70 and PASI75 responses.
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SAT0435 IL17 CORRELATES POSITIVELY WITH TGF-BETA 1 AND DKK1 AND INVERSELY WITH BMP2 AND 4 IN SYNOVIAL MEMBRANE OF PATIENTS WITH PSORIATIC ARTHRITIS

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Background: Immune and non-immune cells contribute to the pathology of chronic arthritis and they can contribute to tissue remodeling and repair as well as disease pathogenesis. An important role for their products such as TGF-beta 1, IL17 or BMPs has been suggested in homeostatic and remodeling mechanisms in arthritis. BMP signaling could have an anti-inflammatory role in the control and maintenance of low levels of pro-inflammatory factors in healthy joints or the early stage of RA.
Objectives: to analyze and compare serum levels, gene expression and immunohistochemistry (IHC) in synovial membrane of inflammation and bone destruction/regeneration biomarkers in patients with psoriatic arthritis (PsA), undetermined seronegative arthritis (USA), Osteoarthritis of the knee (kOA) and ankylosing spondylitis (AS).
Methods: We recruited 45 consecutive patients with chronic knee arthritis referred for undergoing arthroscopies (17 PsA, 12 USA, 12 kOA, 4 AS). Synovial membrane was processed for IHC analysis and quantification of mRNA expression ratio by qRT-PCR. Serum levels of TGF-beta 1, IL6, IL17 and IL22, DKK1, Sclerostin, BMP2, BMP4, Wnt1 and Wnt5a were measured (ELISA). We analyzed and compared these data with the demographic, clinical, analytical and radiological characteristics of the patients. Data were analyzed using the SPSS version 17.0 software and statistical significance was defined as $P<0.05$.
Results: We obtained valid synovial membrane samples from 41 patients for IHC, RNA extraction and purification from 29 patients for analyze mRNA expression and serum from 38 patients for protein levels measurement. IL17 gene expression was higher in PsA patients (p=0.027) and correlated positively with DKK1 (r=0.424, p=0.022) and negatively with BMP2 (r=-0.396, p=0.033) and BMP4 (r=-0.472, p=0.010). IHC reactivity for TGF-beta 1 in synovial tissue was higher in patients with psoriatic arthritis (p 0.010) and correlated positively with IL17 (r=0.389, p=0.012) and DKK1 (r=0.388, p=0.012). Moreover, serum levels of TGF-beta 1 were significantly increased in PsA with erosions (p=0.044).
Conclusions: IL17 gene expression in synovial membrane from patients with psoriatic arthritis was higher than in seronegative undetermined arthritis, osteoarthritis and ankylosing spondylitis patients, correlating positively with DKK1 and negatively with bone morphogenetic proteins 2 and 4. In addition, TGF-beta in synovial tissue, necessary for the activation of Th17 cells, was higher in patients with psoriatic arthritis, in relation to IL17 and DKK1 increased. Serum TGF beta 1 levels were also higher in patients with erosive disease.
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SAT0436 DURABILITY OF APREMILAST RESPONSE IN PATIENTS WITH PSORIATIC ARTHRITIS: LONG-TERM (208-WEEK) RESULTS FROM THE PALACE 1 TRIAL

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Background: Optimizing treatment choice in psoriatic arthritis (PsA) necessitates an understanding of the long-term effects of therapies across varied manifestations of this complex disease. Data from 4 years of apremilast (APR) treatment in PALACE 1 were used to examine disease control across markers of active inflammation, such as SJC, as well as improvements in patient (pt) functionality, as assessed using the HAQ-DI.
Objectives: Evaluate long-term outcomes with APR treatment after ≥1 DMARD or biologic in pts with active PsA.
Methods: Pts were randomized (1:1:1) to placebo (PBO), APR 30 mg BID (APR30), or APR 20 mg BID (APR20). The PBO-controlled phase continued to Wk 24, at which time all remaining PBO pts were re-randomized to APR30 or

APR20. Double-blind APR treatment continued to Wk 52; pts could continue APR for up to 4 additional years in an open-label extension.

Results: 504 pts were randomized and received ≥1 dose of study medication (PBO: n=168; APR30: n=168; APR20: n=168); 86.9% (225/259) of pts entering the third year completed 208 wks of APR treatment; overall, this is 44.6% (225/504) of pts randomized at baseline (BL). At Wk 52, 53.2% of APR30 pts achieved a modified ACR20 response (Table), regardless of when APR was started (BL, Wk 16, or Wk 24). At Wk 208, a sustained response rate was observed in APR30 pts, as shown by an ACR20 response rate of 67.5%. Marked improvements in SJC were seen throughout the study, with a mean percent decrease of −84.2% at Wk 208; TJC reductions were consistent (Table). Functionality is of paramount importance to pts; large improvements were seen in HAQ-DI score, with a mean change of −0.47. Pts also note fatigue as a disease- or treatment-related impairment; a mean improvement of 5.7 was seen in FACIT-F score at Wk 208 (Table), and the pt population reached a mean score of 35.7. In addition, long-term treatment led to the maintenance of the proportions meeting the minimal clinically important difference in HAQ-DI score change, achieving ACR50/ACR70 responses and reaching PASI-75 and PASI-50 responses (Table). No new safety concerns were identified with APR treatment up to 208 wks. During Wks >156 to ≤208, the only adverse event (AE) occurring in ≥5% of APR30-exposed pts was URTI (5.2%); most AEs were mild/moderate in severity. Among APR30-exposed pts, serious AEs occurred in 6.7% of pts in Wks >156 to ≤208, consistent with earlier data. Importantly, few discontinuations due to AEs occurred throughout the long-term treatment period.

Outcomes at Wk 52 and Wk 208		
	Wk 52	Wk 208
	APR30 n=193*	APR30 n=123*
ACR20, n/m§ (%)	101/190 (53.2)	83/123 (67.5)
ACR50, n/m§ (%)	49/191 (25.7)	56/122 (45.9)
ACR70, n/m§ (%)	27/191 (14.1)	35/123 (28.5)
Swollen joint count, mean % change	−50.5	−84.2
Tender joint count, mean % change	−45.1	−78.1
HAQ-DI (0-3), mean change	−0.31	−0.47
HAQ-DI MCID ≥0.30, n/m (%)	85/193 (44.0)	72/123 (58.5)
HAQ-DI MCID ≥0.35, n/m (%)	85/193 (44.0)	72/123 (58.5)
DAS-28 (CRP) <2.6, n/m (%)	41/189 (21.7)	57/122 (46.7)
DAS-28 (CRP), mean change	−1.26	−2.08
FACIT-F, mean change	3.8	5.7
PASI-75‡, n/m (%)	31/95 (32.6)	21/60 (35.0)
PASI-50‡, n/m (%)	52/95 (54.7)	37/60 (61.7)

Data as observed. *The n reflects the number of pts treated with APR30, regardless of when treatment started (BL, Wk 16, or Wk 24), and who had data available at the specific time point; actual number of pts available for each end point may vary. §Denominators vary slightly due to availability of sufficient data for each level of ACR response assessment. ‡Examined among pts with psoriasis involvement of the body surface area ≥3% at BL and data at the specific time point. APR30=apremilast 30 mg BID; ACR20/50/70=20%/50%/70% improvement in modified American College of Rheumatology response criteria; n/m=number of responders/number of pts with sufficient data for evaluation; HAQ-DI=Health Assessment Questionnaire-Disability Index; MCID=minimal clinically important difference; DAS-28=28-joint count Disease Activity Score; CRP=C-reactive protein; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; PASI-75/50=≥75%/≥50% reduction from BL Psoriasis Area and Severity Index score; pts=patients; BL=baseline.

Conclusions: APR30 demonstrated sustained, clinically meaningful improvements in signs and symptoms of PsA, physical function, and associated psoriasis over 208 wks. APR30 continued to demonstrate a favorable safety profile and was generally well tolerated.

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SAT0437 IXEKIZUMAB IMPROVES NAIL AND SKIN LESIONS IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND PRIOR TNF INADEQUATE RESPONSE

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Background: Ixekizumab (IXE), a high-affinity monoclonal antibody selectively targeting interleukin-17A, significantly improved fingernail psoriasis by Week (Wk) 12 vs placebo (PBO) in patients (pts) with moderate-to-severe plaque psoriasis[1]. Moreover, IXE had significantly reduced signs and symptoms of psoriatic arthritis (PsA) at Wk 24 in biologic disease-modifying antirheumatic drug (bDMARD)-naïve pts with active PsA[2].

Objectives: To evaluate the impact of IXE on nail and skin lesions in active PsA pts who have previously received bDMARD therapy.

Methods: In this phase 3, multicentre, double-blind, PBO-controlled, outpatient study, pts (aged ≥18 years) with active PsA and bDMARD-experience randomly (1:1:1) received PBO for 24 Wks, 80 mg IXE as one injection every 2 (IXE Q2W) or 4 Wks (IXE Q4W) after starting dose of 160 mg. At Wk 16, inadequate responders received rescue medication and PBO pts were re-randomised (1:1) to receive either IXE Q2W or IXE Q4W. The efficacy of IXE was assessed by Nail Psoriasis Severity Index (NAPSI) in pts with nail psoriasis at baseline (PBO, n=73; IXE Q4W, n=89; IXE Q2W, n=74), Psoriasis Area and Severity Index (PASI) 75/90/100 response rate at Wk24 in pts with baseline body surface area (BSA) ≥3 (PBO, n=67; IXE Q4W, n=68; IXE Q2W, n=68) and percentage of pts achieving static Physician Global Assessment (sPGA) of psoriasis score of 0 (cleared) or 1 (minimal) in pts with baseline sPGA≥3 (PBO, n=55; IXEQ4W, n=60; IXEQ2W, n=62). Missing data and inadequate responder data were imputed using the nonresponder imputation for categorical variables. For continuous variables, least squares mean (LSM) changes were calculated using mixed effects models for repeated measures, observed data from Wks 16 to 24 was excluded for inadequate responders.

Results: Overall the demographics and baseline characteristics were comparable between the treatment groups. The mean (SD) NAPSI total score at baseline was 19 (19), 20 (20), and 21 (22) in PBO, IXE Q4W and IXE Q2W, respectively. At Wk 24, the change in NAPSI total score from baseline was significantly greater with IXE Q4W (LSM±SE -10.2±2.04) and IXE Q2W (-10.8±2.12) vs PBO (0.5±2.13, p<.001 each). Similarly, the mean percentage improvement in NAPSI total score was significantly greater with IXE Q4W (LSM±SE 35.4±22.14, p<.001) and IXE Q2W (30.9±22.95, p=.001) vs PBO (-45.2±23.04). At Wk 24, significantly greater percentage of pts achieved a NAPSI score of 0 with IXEQ4W or IXEQ2W treatment vs PBO (Table). At Wk 24, the percentage of pts achieving PASI 75/90/100 response was significantly greater with IXE Q4W and IXE Q2W vs PBO (Table). Overall, the safety profile of IXE was aligned with the general study population.

Table: Percentage of patients with improvement in skin and nail lesions

Efficacy endpoints (%)	Placebo	IXE Q4W	IXE Q2W
PASI 75[a]	14.9	55.9*	60.3*
PASI 90[a]	11.9	44.1*	50.0*
PASI 100[a]	4.5	35.3*	27.9*
sPGA (0, 1)[b]	9.1	66.7*	75.8*
NAPSI (0)[c]	6.8	20.2**	29.7*

*p<.001; **p=.022; [a]Patients with baseline ≥3% BSA; [b]in patients with baseline sPGA ≥3; [c]Patients with baseline fingernail psoriasis

Conclusions: In the present study, ixekizumab led to significantly greater reduction and clearance of the nail and skin lesions in active PsA pts who had previously received bDMARD therapy compared to placebo.

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