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RESEARCH ARTICLE

JAK INHIBITORS AS A NEW MODALITY FOR TREATING ATOPIC DERMATITIS: A BETTER UNDERSTANDING OF ITS EFFICACY AND SAFETY

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Abstract

AD is a chronic relapsing disease characterized by pruritis and chronic inflammatory skin changes, [(1)] which affects approximately 10–30% of children and as much as 10% of adults worldwide.[(2)] This condition has a great significant impact on morbidity and presents an outstanding social economic burden.[(3)] AD is a multifactorial disease that develop by interaction between these factors in a positive feedback cycle.

Treatment of AD interrupts the causal pathway. Management with conventional therapies has been a challenge, but a novel biological treatment called dupilumab was recently approved for the treatment of moderate-to-severe AD, but this drug only achieved 40% clear skin in combination with TCs.[(4)]

JAK inhibitors are another new drug family that inhibit JAK-signaling pathways, which involve JAK1, JAK2, JAK3 and TYK2. JAK inhibitors have been approved to treat inflammatory diseases like rheumatoid arthritis, and high attention is currently being focused on the clinical development of JAK inhibitors for the treatment of AD. Which are a possible treatment for certain disease that are related to lymphocyte activation, such as psoriasis, alopecia areata, vitiligo and AD. JAK inhibitors are available in topical and oral forms, thereby allowing more administration routes depending on the severity of AD, which ranges from mild to severe. Since JAK inhibitors are a new treatment modality in dermatology, the efficacy of this new medicine and the safety thereof are still being debated.

A systematic review and meta-analysis were done for all randomized clinical trials that evaluated JAK inhibitors for Atopic dermatitis to investigate their pooled efficacy and safety compared to placebo. Results might be useful as a milestone to develop a more accurate view of this medication and provide direction for further research.

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Introduction:-

Objectives:-

Corresponding Author:- Dr. Abdullah Alnama

The aim of this study is to use the primary research found in different databases to assess the effectiveness of using JAK inhibitors to improve atopic eczema disease, compared to other treatment protocols or no treatment (placebo) and to evaluate and weigh the drug associated complications.

Research question

What is the efficacy and safety of using JAK inhibitors in treating atopic eczema patients compared to placebo or other treatment protocols?

Methods:-

A detailed search for literature in various databases (i.e., CINAHL, AMED and PubMed) on the use of JAK inhibitors for treating moderate-to-severe AD and a critical analysis of the selected papers in relation to the efficacy of the drug, as well as complications that have been encountered. A detailed bibliography will be presented at the end of the study.

Results:-

A total of 10 RCTs (six for oral JAK inhibitors and four for topical JAK inhibitors) were included. Patients were randomized into placebo groups (n = 817) and JAK-inhibitor groups (n = 1795). All oral an d topical JAK inhibitor trials were pooled together and associated with clinical improvement of AD cases detected by EASI 50 RR = 3.23 (95%, CI 2.41–4.32), IGA 0–1 RR = 2.98 (95%, CI 2.02–4.42) and for Pruritus NRS = 3.64 (95%, CI 1.72–7.73). Separate measurements of RR for oral and topical JAK trials yielded similar statistically significant results, which denotes that both are effective for treating AD. AD patients (orally or topically treated with JAK inhibitors, pooled together) were not at a significantly higher overall risk for AEs (RR 1.05 [95%, 0.87–1.26] P = 0.0009, χ^2 = 26.47, I2 = 70%). A total of seven studies evaluated serious AEs, with a pooled-RR of 0.75 [95%, CI 0.41–1.38] (P = 0.84, χ^2 = 2.08, I2 = 0%) denoting protective effect but this protection is statistically insignificant.

Conclusion:-

JAK inhibitors are effective, novel medications that lead to significant improvements when treating moderate-to-severe AD with overall tolerated safety.

Methodology:-

This thesis includes a systematic review and meta-analysis and is designed as follows:
The strategy for addressing the research question involves the fundamental step of a systematic review and meta-analysis of the selected primary studies. Followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for proposal development and to systematize the conduct of this study.[5] Figure 1 shows the steps that were followed in this study, and Table 1 provides a summary of the PICOS (Population, Intervention, Comparator, Outcome and Study design).

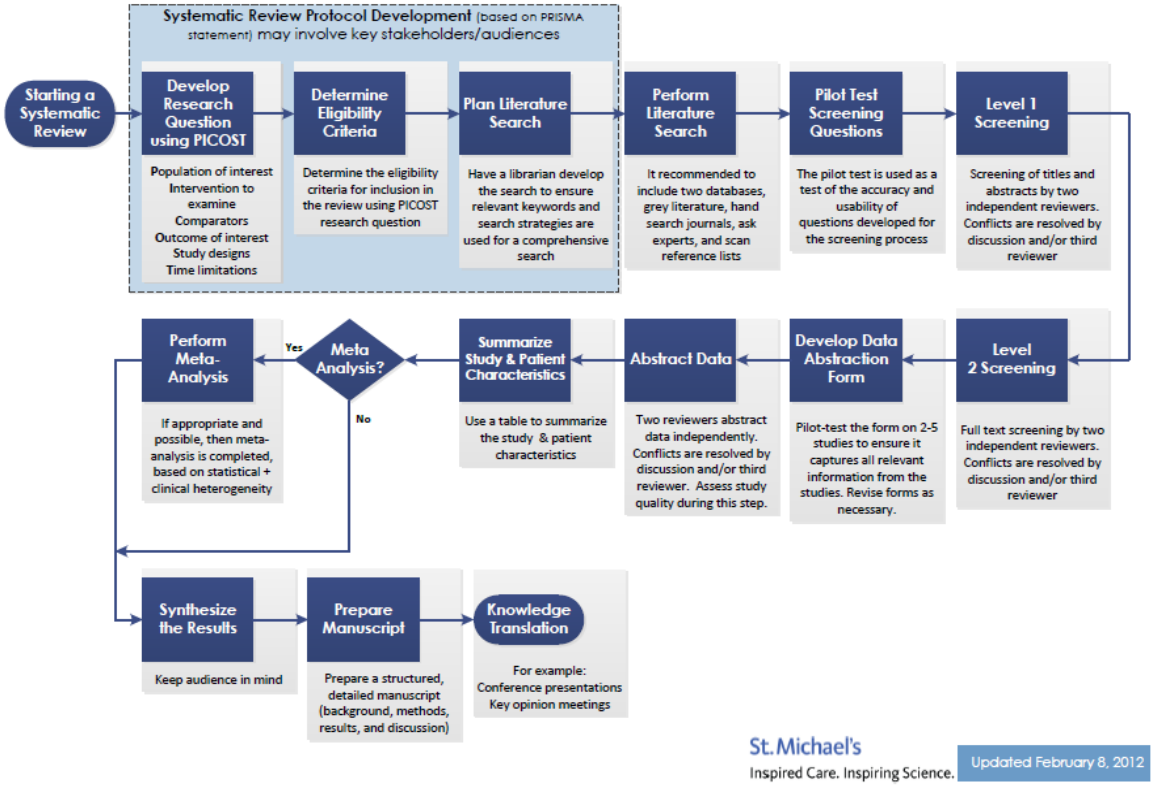

Figure1:- Systematic review executive flowchart.

Table1:- PICOS of the systematic review.

Population	Mild to severe adult patients with AD
Intervention	Treatment with any protocol, including JAK inhibitors (topical or systemic)
Comparison	No management (placebo) or other treatment protocols
Outcome	Primary outcome: Disease improvement measures (discussed later) Secondary outcome: Complications and safety (AEs, infections, etc.)
Study design	I will include randomised controlled trials

Inclusive criteria of studies

Population included: The included population is adult patients diagnosed with mild, moderate or severe AD who received topical or systemic JAK inhibitors in order to assess the efficacy of treatment. There are no sex or location limitations. Studies conducted on pediatric patients are excluded.

Interventions: Application of any of the JAK inhibitors, including topical or systemic routes, to assess the efficacy and/or safety in managing AD patients compared to placebo..

Comparator:
All studies included in the analysis used a placebo in the control group as a comparator.

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Outcomes
A review of the literature is conducted to get comprehensive view of the clinical measures that can be used for AD assessment. Outcomes are selected as a standardized measure for evaluating AD patients. The novel drug is directly and indirectly evaluated by the primary and secondary outcomes.

Primary outcomes include:
1. Improvement detected by achieving an EASI 50 score
2. Improvement detected by reaching IGA 0–1 or ≥ 2-point reduction from baseline
3. Reduction of POEM score by four or more points from standard line
4. Improvement of four or more points below the baseline in the peak pruritus NRS score

Many studies were reviewed to determine the most appropriate secondary outcomes to enhance accuracy and standardize assessments of the safety of JAK inhibitors. Identified secondary outcomes included : [6-9]

1. Treatment of emergent AEs (TEAE)
2. Serious AEs
3. AE-related withdrawal
4. Infectious AEs
5. Significantly infectious AEs

Types of studies
We only included randomized controlled phase-2 and -3 trials to ensure the high quality of our primary studies. Any extended Open-label studies with no placebo used were excluded.

Language: Only studies written in English will be included in this review.

Search Strategy
A three-step strategy is used to find published and unpublished studies on AD-related JAK inhibitor trials. First, We conducted an initial search through the Medline Ovid database using an analysis of text words found in the title and abstract, and the index terms used to describe the article. Keywords and index terms are then identified to search for studies in other databases. Finally, the reference list of selected studies from the first and second searches is used to seek out additional studies not found in the databases. Only published or unpublished studies in grey literature were considered for the current study and revealed no studies to be included.

In this review we search the Medline Ovid (1946–2020), PubMed (1990–2020), Scopus (1999–2020) and Web of Science (1900–2020) databases. The keywords we used for our initial searches in Medline Ovid are ‘Atopic dermatitis’, ‘Atopic eczema’, ‘JAK inhibitors’, ‘mild to severe cases’, ‘neurodermatitis’, ‘Janus kinase’, ‘Tofacitinib’, ‘Ruxolitinib’, ‘Baricitinib’, ‘Upadacitinib’, ‘PF-04965842’, ‘ASN002’ and ‘Delgocitinib’.

Study Screening and Selection
The PRISMA flow diagram in Figure 2 illustrates the different steps for screening studies. All citations that result from the search of databases are imported to Covidence software program to remove duplicated studies, and inclusion and exclusion criteria were also uploaded to the program. Two researchers, Abdullah Alnama (AN) and Hassan Mahmood (HM), are responsible for screening the titles and abstracts as a first step for study selection, and all discrepancies between the two researchers are resolved by discussion to reach consensus. Full texts of selected abstracts are retrieved by the software to begin the second step by the same researchers, which includes full text review to determine eligibility according to the inclusion and exclusion criteria outlined above, and any contradictions are resolved by open discussion.

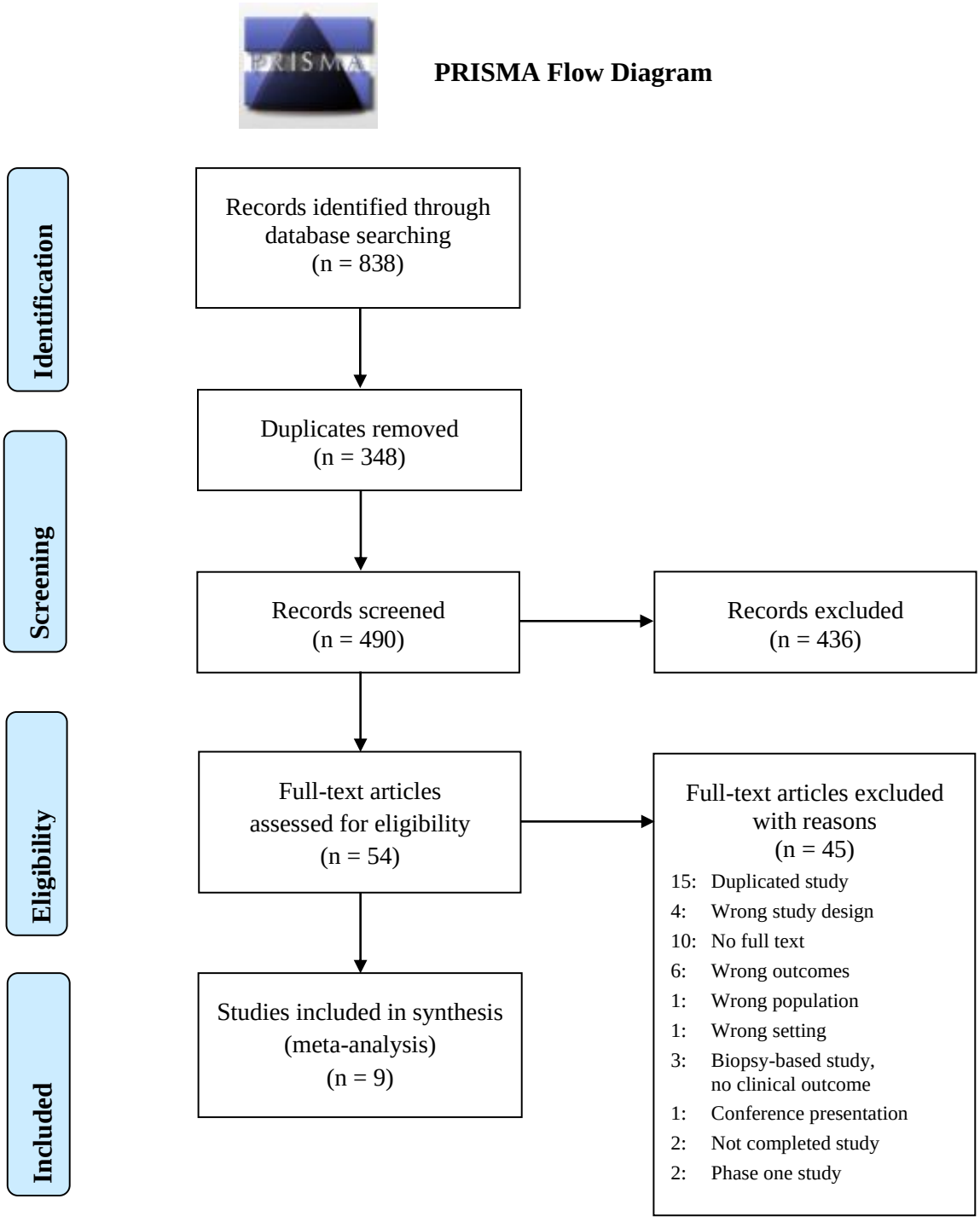


Figure2:- Prisma flow diagram.

Data Extraction

After screening selected studies and assessments, key information from these studies is extracted into an Excel spreadsheet that is derived from the standardized data-extraction tool for quantitative studies devised by the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). In order to increase accuracy of extracted data, two independent reviewers (AN and HM) were assigned to extract data using a standardized electronic data collection form. Discrepancies are resolved by consensus.

Extracted information includes:

1. Study characteristics of reviewed papers, such as authors, years of publication and the name of the publishing journal
2. Methods of the study, including study design (RCT, quasi-RCT, Longitudinal, retrospective) and research purpose and/or questions
3. Participant characteristics, country where the study took place, setting, population, sample size, age and sex
4. Interventions used to treat AD in the experimental and control groups, including the dosages (if applicable)
5. Outcome measures and results
6. Conclusions of reviewed papers and any comments from reviewers.

For primary outcomes, clinical outcomes are assessed using the EASI scoring method. Clinical response defined by a EASI score ≥ 50 are extracted and compared to the baseline. Primary studies that made few modifications for EASI way of measurement and were not expected to demonstrate significant difference from regular EASI were included. Clinical response defined by an IGA 0–1 or ≥ 2-point reduction from baseline are also extracted. Patient-Oriented Eczema Measure (POEM) showing a reduction of four or more points from the baseline are indicated as a primary outcome and are extracted from one study. Finally, the Peak Pruritus Numerical Rating Scale-11 (NRS-11) showing an improvement of four or more points from the baseline are extracted from three studies that assessed oral JAK inhibitors. The DLQI with an improvement of ≥ 4 points reduction from baseline are not measured in any of the included studies. Different definitions for outcomes were found in primary studies of atopic dermatitis. To overcome this problem, It was standardized through the use of above definitions and extracted data based on that to allow for comparisons between these trials.

For secondary outcomes, safety was assessed by extracting the proportions of patients who got any of the following events: adverse Events (AE) or serious AEs (SAE) or quit the study due to AE or infections related adverse events or worsening Atopic dermatitis. In addition, We collected the number of cases who experienced herpes zoster (HZ), serious events such as cancer or death. AEs that occurred during parts of studies were placebo was not used as a comparator was not included.

Serious adverse events (SAEs) are defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability and/or incapacity, results in a congenital anomaly and/or birth defect or if appropriate medical judgment deems it as an important medical event that may jeopardize the health of the research participant or may require medical intervention to prevent one of the outcomes listed above.[9] It is also important to define serious infectious AEs, as these are infections that lead to death or hospitalization or require intravenous antibiotics. [10]

Data Synthesis

In order to compare treatment effect between intervention groups and placebo groups We used the relative risk (RR) for efficacy and safety as well. We used intention to treat principles with calculation of risk ratio with 95% confidence interval. A RR<1 will represent a lower rate of outcome among the group of patients who were treated with JAK inhibitors. For studies that assessed effects of different doses of JAK inhibitors on patients, We pooled all the data together. Because of the expected heterogeneity of data collected, We used a random-effects model to pool these data. The random effect is based on what is called the DerSimonian and Laird method which consider different types of heterogeneity within- and between-studies. [11] This will account for the heterogeneity between study populations given the pooling of different therapies and doses. Chi-square test was used to test the heterogeneity. In addition, between study heterogeneity was evaluated using the I^2 metric. It indicates the percentage of the total variation across studies. The following thresholds for I^2 interpretation were used in accordance with the Cochrane Handbook for Systematic Reviews of Interventions: 0%–40% (may not be important), 30%–60% (moderate heterogeneity), 50%–90% (substantial heterogeneity), 75%–100% (considerable heterogeneity). Potential publication bias was not formally evaluated by funnel plots as less than 10 studies were identified for both of Oral and topical JAK inhibitors.

All analyses were conducted in review manager 5.3. All *P*-values are two-tailed and $P < 0.05$ indicates statistical significance.

Systematic Review and Meta-Analysis Results

Database Search Resultsand Characteristicsof Selected Studies

A total of 838 records were identified through searching different databases. Removing duplicates was done and ended up with 490 records. These records were screened and 436 studies were found to be ineligible and excluded based on reviewing the title and abstract; in final step which is full text assessment (see Figure 2) 44 records were excluded for the following reasons:

1. 14 were duplicated
2. The full text for 10 studies could not be found
3. Four had the wrong study design
4. Nine showed the wrong outcomes with three of using biopsy for their outcome assessment
5. One had the wrong population (pediatric patients)
6. One was in the wrong setting
7. One was a conference presentation
8. Two were phase-1 studies
9. Two were incomplete
   10 placebo controlled RCTs were eligible for inclusion in the systematic review and meta-analysis, [118-125] but two independent trials of these RCTs were conducted in one study [20]
10. Six evaluated patients on oral JAK inhibitors [13-16, 20]
11. Four trials evaluated patients on topical JAK inhibitors [118, 123-125]
    These trials and their baseline patient characteristics are summarized in Table 2.

The included studies were conducted in countries located in Europe, North and Latin America, Asia and Australia. Participants in the studies were vitally stable adult patients (18–65 years of age). Details about the studies are also summarized in Table 2. A total of 2612 AD patients, including 1085 (41.5%) females, were randomized: 1795 to intervention groups with a JAK inhibitor, and 817 to control groups. Only two trials were found to assess JAK1-selective inhibitors (Upadacitinib[16] and Abrocitinib[14]) and seven trials that assessed pan-JAK inhibitors (tofacitinib,[12] Gusacitinib,[13] Baricitinib,[121] RUX,[17] Delgocitinib [18,19] and Baricitinib. [20]

Table2 Baseline characteristics of included randomized controlled trials assessing efficacy and safety of JAK inhibitors in treating atopic dermatitis disease.

Author (Year)	Study Design	Duration	Location	Sample size	Mean sample age* Int:Ctl** Y±SD	Population: Gender Int:Ctl** No. (%)	Intervention	Dose	Frequency	Outcome	JAK Type
Bissonnette (2016)	RCT: Phase2a	4weeks	Canada	69	32.4±9.8: 30.4±10.4	Female: 19(54.3): 18(52.9) Male 16(45.7): 16(47)	Tofacitinib	Ointment2%	BID	EASI, adverse events	Topical JAK1/ JAK2/ JAK3
Bissonnette (2019)	RCT	4weeks	Canada United States	36	37.9±13.09: 29.9±9.33	Female 12(44.4): 6(66.7) Male 15(55.6): 3(33.3)	Gusacitinib	20mg/40mg/80	QD	EASI,IGA, Pruritus NRS, adverse events	OralJAK/ spleen tyrosine kinase inhibitor

Gooderham (2020)	RCT: Phase2b	12weeks	Australia Canada Germany Hungary United States	267	40.43±16.25: 42.6±15.1	Female 109(51.7): 35(62.5) Male 02(48.3): 21(37.5)	Abrocitinib	200mg 100mg 30mg 10mg	QD	IGA,EASI, Pruritus NRS,TEAE,LAB results and vital signs	Oral JAK1
Guttman-Yassky (2019)	RCT: Phase2	16weeks	United States Japan	124	Median 37.25:35	Female 31(41.3): 25(51) Male 44(58.7): 24(49)	Baricitinib with TCS***	2mg 4mg	QD	EASI,DLQI,IGA,POEM	Oral JAK1/JAK2
Guttman-Yassky (2020)	RCT: Phase2b	16weeks	Australia Canada Finland Germany Japan Netherlands Spain United States	167	Int40±15.3: 39.9±17.5	Female 46(36.5): 17(41.5) Male 80(63.5): 24(58.5)	Upadacitinib	7.5mg 15mg 30mg	QD	EASI,IGA,POEM,DLQI,TEAE	Oral JAK1
Kim (2020)	RCT: Phase2	8weeks	United States Canada	307	Median 36.9:31.5 TAC35	Female 108(52.9): 32(61.5) TAC 28(54.9) Male 96(47.1): 20(38.5)	RUX or TAC***	(0.15%RUX/ 0.5%RUX/ 1.5%RUX) (1.5% RUX))	QD BID	EASI,IGA, TEAE	Topical JAK1/JAK2
Nakagawa (2018)	RCT: Phase2	4weeks	Japan	326	Int 30.37±9.75 Ctl 31.6±9.6 TAC 33.1±11.6	Female 88(33.2): 12(38.7) TAC 16(53.3) Male 177(66.8): 19(61.3)	Delgocitinib or TAC***	0.25% 0.5% 1% 3%	BID	EASI,IGA, face/neck IGA, pruritus NRS,BSA,TEAE	Topical JAK1/JAK2/JAK3

						TAC 14(46.7)					
Nakagawa (2020)	RCT: Phase3	4weeks	Japan	158	Int 31.4±9.6 Ctl 32.3±11.2	Female 42(39.6): 18(34.6) Male 64(60.4): 34(65.4)	Delgocitinib	0.50%	BID	EASI,IGA, face/neck IGA ,pruritus (NRS),BSA,andSkindex-16,TEAE	Topical JAK1/JAK2/JAK3
Simpson BREEZE1 (2020)	RCT: Phase3	16weeks	Europe Asia Latin America Australia	624	36±13: 35±12.6	Female 132(35.2): 101(40.6) Male 243(64.8): 148(59.4)	Baricitinib	4mg 2mg 1mg	QD	IGA,POEM,DLQI, itch NRSe, EASISCORAD, affected BSA, skin pain, NRSf, ADSS	Oral JAK1/JAK2
Simpson BREEZE2 (2020)	RCT: Phase3	16weeks	Europe Asia Latin America Australia	615	34.3±12.43: 35±13	Female 144(38.8): 90(36.9) Male 227(61.2): 154(63.1)	Baricitinib	4mg 2mg 1mg	QD	IGA,EASISCORAD, affected BSA,itch NRSe,NRSf, POEM, ADSS, DLQI, skinpain	Oral JAK1/JAK2

*** Mean age is reported in years (Y) ± standard deviation (SD), unless described as median age. ** Int. is the intervention groups pooled together, and Ctl. is the control group. *** TCs is topical corticosteroids; TAC is tacrolimus.**

Assessment of methodological quality and risk of bias

The quality of the nine selected studies was independently assessed by researchers AN and HM. The standard critical appraisal tools for quantitative studies devised by the JBI-MAStARI Methodological was used to determine the validity of the selected papers for retrieval, as shown in Table 3. All disagreements between the two reviewers were solved through discussions.

Assessment of study validity revealed few sources of bias. All studies reported treatment randomisation and blinding of participants. All studies concealed allocation to treatment groups. Withdrawn participants were considered in the analysis of outcomes in six studies, but this was unclear in Nakagawa et al. (2020); not reported in Nakagawa et al. (2018); and incomplete in Simpson et al. (2020). A majority of the included studies—five of nine—did not clearly report that outcome assessors were blind to treatment. All studies except for Simpson et al. (2020) showed comparable intervention groups to placebo group in which this criterion was partially met. All the studies that fulfilled the inclusion criteria were included after a methodological quality assessment, as they all achieved > 75% in the JBI-MAStARI criteria.

Table3:- Quality assessment of selected studies using JBI-MAStARI.

Author	Year	Treatment assigned randomly	Participants blinded to treatment	Treatment group allocation concealed	Withdrawn participants outcome included in analysis	Outcome assessors blind to treatment	Comparable control and treatment groups	Groups treated identically, other than intervention	Outcome measured the same for all groups	Outcome measured in a reliable way	Appropriate statistical analysis used	Include or exclude
Bissonnette	2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Bissonnette	2016	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Include
Gooderham	2020	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Include
Guttman-Yassky	2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Include
Guttman-Yassky	2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Kim	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Nakagawa	2019	Yes	Yes	Yes	No	Notclear	Yes	Yes	Yes	Yes	Yes	Include
Nakagawa	2020	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Include
Simpson	2020	Yes	Yes	Yes	Incomplete	Yes	Partially	Yes	Yes	Yes	Yes	Include

Efficacy of Topical and Oral JAK Inhibitors

Topical JAK inhibitors

Four included studies assessed the efficacy of topical JAK inhibitors compared to placebo. One study conducted by Bissonnette et al. (2016) investigated the effect of applying tofacitinib ointment at a mean application rate per 2.4mg/cm^2 dose, compared to the placebo mean rate of 2.5mg/cm^2 for four weeks. It was determined that the improvement measured by reaching EASI 50 in patients receiving tofacitinib is three times greater than in the placebo group (RR = 3, CI 1.84–4.9), and the proportion of patients achieving EASI 50 and EASI 75 responses was significantly higher for tofacitinib versus placebo at all time points ($P < 0.05$).

In another study, Kim et al. (2020) demonstrated that application of all concentrations of RUX cream resulted in statistically significant improvement from baseline EASI scores versus placebo at each time point (weeks 2, 4 and 8) of the double-blind period. RUX cream demonstrated increasing improvement over time and with higher concentrations. The study revealed that 78% achieved EASI 50 at week four for the RUX 1.5% BID group, compared to 23.1% in the placebo group, which is a statistically significant difference in treating AD. The study also assessed patients achieving IGA 0–1 outcome in the different study groups compared to placebo group and showed that the chances of AD patients achieving IGA 0–1 are 2.68 times higher with RUX treatment than with a placebo.

Nakagawa et al. (2018) and a study by Nakagawa and a different team (2020) included phase-2 and phase-3 RCTs to assess the efficacy and safety of Delgocitinib. Both studies showed a statistically significant difference between the proportion of patients receiving the medicine and achieving EASI 50 compared to placebo groups, with risk ratios 2.96 and 4.5, respectively. When IGA 0–1 was used to assess improvement in the 2018 study, similar results were found with a risk ratio of 4.21 and CI 0.6–29.66; however, these findings were not statistically significant from placebo.

The result of the meta-analysis of pooled data from the four included studies was highly homogenous—I^2 = 0%, and showed a statistically significant effect of the topical use of JAK inhibitors to treat AD, as shown by the two recorded primary outcomes: EASI 50 and IGA 0–1 with RR = {3.29 (2.46, 4.39) χ^2 = 0.9 P = 0.83} and {2.93 (1.22, 7.04), χ^2 = 0.17 P = 0.68}, respectively, compared to the placebo (see Figures 3 and 4).

Oral JAK inhibitors

The research for primary studies detected five RCTs that evaluated the efficacy and safety of orally administered JAK inhibitors to treat AD patients. In an RCT conducted by Bissonnette et al. (2019), a total of 36 patients were randomised. The proportion of patients achieving EASI 50 at day 29 was significantly higher for patients receiving gusacitinib in 40mg (100%, P = 0.003) and 80mg (83%, P = 0.03) doses, but not 20mg (20%, P = 0.93) doses, compared with placebo (22%), with all pooled groups achieving RR = 3.17 (0.91, 11.01), which is statistically insignificant. The proportion of patients achieving IGA 0–1 with at least a two-point reduction from baseline at day 29 was not statistically significant for different intervention groups compared with placebo: 43% (P = 0.16) for patients receiving a 40mg dose of gusacitinib, 17% (P = 0.77) for patients receiving an 80mg dose of gusacitinib, 0% (P = 0.46) for patients receiving a 20mg dose of gusacitinib, and 11% for patients receiving placebo, with pooled RR = 2(0.28, 14.46).

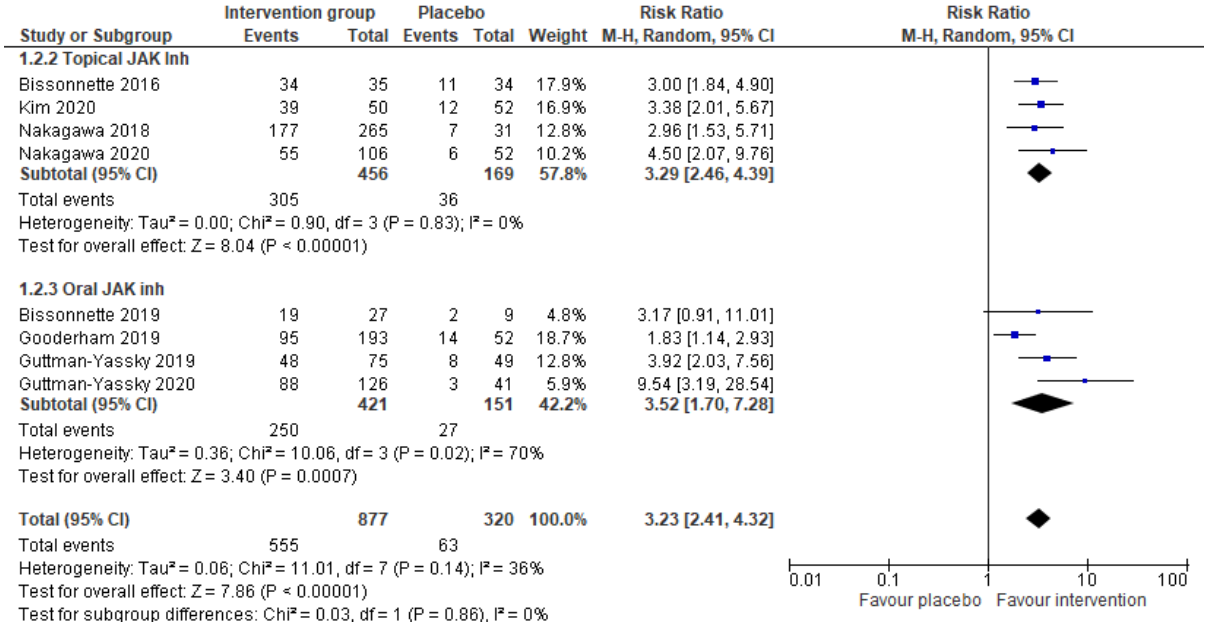
A study conducted by Gooderham et al. (2019) investigated the efficacy and safety of abrocitinib to treat AD. EASI 50, IGA 0–1 with a two-or-more-point improvement from baseline and Pruritus NRS were used as efficacy outcomes. Proportions of patients who achieved EASI 50 at week 12 showed a statistically significant difference 55.6%, and 79.2% at doses of 100mg and 200mg, respectively, compared to 26.9% for the placebo group; while proportions for groups receiving 10mg (26.1%) and 30mg (33.3%) doses were insignificant statistically. Their collected RR = 1.83 (1.14, 293) was significant. At the same week, in 21 of 48 (43.8%) patients receiving 200mg of abrocitinib, 16 of 54 (29.6%) patients receiving 100mg of abrocitinib, four of 45 (8.9%) patients receiving 30mg of abrocitinib, five of 46 (10.9%) patients receiving 10mg of abrocitinib and three of 52 (5.8%) patients receiving placebo achieved the primary outcome of IGA0-1 with overall RR = 4.13 (1.34, 12, 75), which is statistically significant. For a Pruritus NRS score with ≥ four-point improvement, the groups receiving 10mg, 30mg, 100mg and 200mg showed the following proportions 22.7%, 33.3%, 50% and 63.3%, respectively, compared with 25.5% for placebo, which denotes similar findings with an insignificant overall RR = 1.62 (0.98, 2.67).

Two studies conducted by Guttman-Yussky et al. [15,16] investigated the efficacy of the oral JAK inhibitors baricitinib and upadacitinib, respectively. The collective result of the proportions of EASI 50 in the intervention groups to placebo group were statistically significant 64% to 12.33% in 2019, and 69.8% to 7.3% in 2020, with a collective RR = 3.92 (2.03, 7.56) for year 2019 and 9.54 (3.19, 28.54) in 2020. Proportions achieving IGA 0–1 with a two-or-more-point improvement from baseline was also used to evaluate efficacy in both studies: 12% in the intervention groups compared to 2% in placebo with RR = 5.88 (0.77, 44.97) in 2019, which was statistically insignificant, and 31.7% to 2.4% in 2020 with statistically significant RR = 13.02 (1.85, 91.74). The 2020 RCT measured the proportions of patients who achieved pruritus NRS score with a four-or-more-point improvement from baseline: 54% in intervention groups compared to 4.9% in placebo group with a significant RR = 11.06 (2.84, 43.16).

The final study included in the evaluation of the efficacy of oral JAK inhibitor Baricitinib was conducted by Simpson et al. (2020) in which two RCTs—BREEZE1 and BREEZE2—were conducted and showed similar findings to the previously mentioned studies with statistically significant proportions of patients achieving IGA 0–1 with a two-or-more-point improvement from the baseline in the intervention groups compared to placebo group: 7.7% to 2.8% with RR = 2.75 (1.22, 6.18) in BREEZE1 and 9.4% to 4.1% with RR = 2.3 (1.16, 4.56) in BREEZE2; both are statistically significant. Regarding the results for proportions of patients achieving a Pruritus NRS score with a four-or-more-point improvement, the intervention groups showed 14.7% compared to 4% in in placebo group for BREEZE1 with RR = 3.65 (1.9, 7.03), and 13.5% to 2.9% in BREEZE2 with RR = 4.7 (2.17, 10.19); both are statistically significant.

Meta-analysis of the five included studies (see Figures 3, 4 and 5) showed significant effects of orally administered JAK inhibitors when compared to placebo, as demonstrated by RR for EASI 50 = 3.52 (1.7, 7.28), IGA 0–1 RR = 3 (1.93, 4.65) and Pruritus NRS RR = 3.64 (1.72, 7.73).

Meta-Analysis for the Efficacy of Topical Versus Oral JAK Inhibitors Figures 3, 4 and 5 demonstrated the pooled efficacy of oral and topical JAK inhibitors derived from included studies separately and collectively. It is clear from tables that the efficacy of oral JAK inhibitors is expected to be higher than the topical JAK inhibitors as shown by RR for EASI 50 = 3.52 (95%, CI 1.7–7.28) compared to 3.29 (95%, CI 2.46–4.39) in topically administered drugs, RR for IGA 0–1 = 3 (95%, CI 1.93–4.65), compared to 2.93 (95%, CI 1.22–7.04) in topically applied medicine. It is also important to note that oral and topical JAK inhibitors are both significantly effective in improving AD patients with overall pooled RR for EASI 50 = 3.23 (95%, CI 2.41–4.32), for IGA 0–1 = 2.98 (95%, CI 2.02–4.42) and for Pruritus NRS = 3.64 (95%, CI 1.72–7.73).



*Kim et al., 2020, didn't mention No. of patients who achieved EASI 50 in different intervention groups in their published paper or attached documents, I included the only available result of proportions in intervention groups achieving EASI 50 compared to the placebo group.

Figure3:- EASI 50topical vs. oral JAK inhibitors.

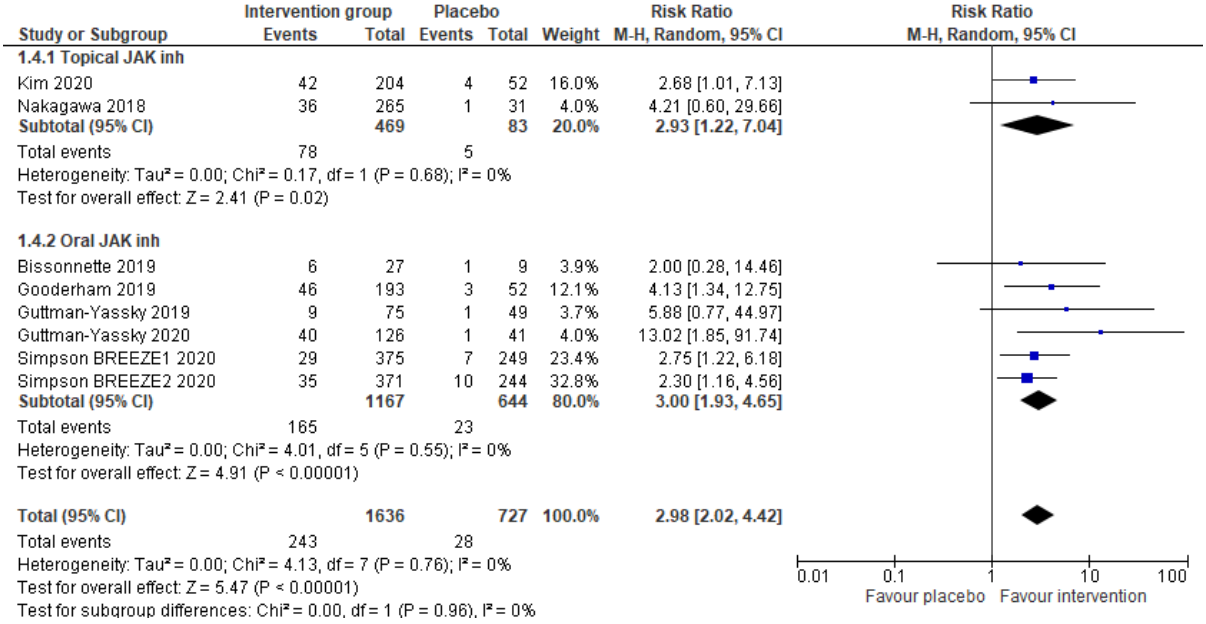
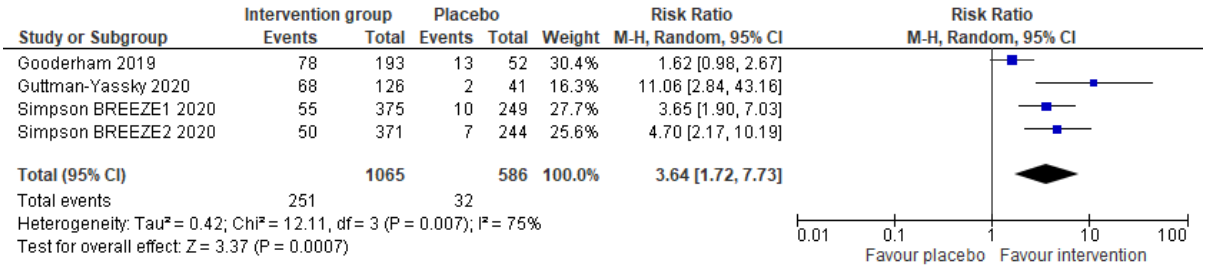


Figure4:- IGA 0–1 topical vs. oral JAK inhibitors.



*All included studies that measured NRS were assessing the efficacy of oral JAK inhibitors.

Figure5 Pruritus NRS

Safety of Topical and Oral JAK Inhibitors

Table 4 summarizes the safety of JAK inhibitors in intervention groups compared to control groups. There is no significant increase in overall risk for adverse events in atopic dermatitis patients who got JAK inhibitors (orally and topically treated pooled together) with RR= 1.05 [95% CI 0.87-1.26] $P = 0.0009$, $\chi^2 = 26.47$, $I^2 = 70\%$ (see Figure 6). Only Bissonnette et al. (2016) showed a statistically significant protective effect for the use of topical tofacitinib in the treatment of AD with RR = 0.45 (95% CI 0.27–0.74); while Gooderham et al. (2019) reported more of a statistically significant risk for the orally administered JAK inhibitor in the intervention groups than in placebo group with RR = 1.55 (95%, CI 1.23–1.96).

TEAE are undesirable events that were not present prior to starting a medical treatment. The meta-analysis for TEAE showed that the pooled-RR for orally administered JAK inhibitors RR= 1.12 (95%, CI 0.95–1.34) $P = 0.02$, $\chi^2 = 12.07$, $I^2 = 67\%$ is slightly higher than in the topically applied groups RR = 0.91 (95%, CI 0.51–1.65) $P = 0.01$, $\chi^2 = 10.93$, $I^2 = 73\%$; however, none of them are statistically significant. A total of seven studies evaluated serious AEs, with a pooled-RR 0.75 ([95%, CI 0.41–1.38] $P = 0.84$, $\chi^2 = 2.08$, $I^2 = 0\%$), which denotes a protective effect but is statistically insignificant (see Figure 9). Study quit and withdrawals due to adverse events in intervention groups showed roughly similar risks compared to placebo groups (RR 1.01 [95%, CI 0.65–1.58]). In contrast, six included studies evaluated infectious AEs, results showed no significant increase in risk of infections (RR =1.31 [95%, CI 0.94–1.83] $P < 0.01$, $\chi^2 = 16.07$, $I^2 = 63\%$). Only two studies reported a significantly increased risk of infections in the intervention groups compared to the placebo groups, Bissonnette et al. (2019) and Guttman-Yassky et al. (2020), with RR 1.82 (95%, CI 1.1–3) and 2.26 (95%, CI 1.18–4.33), respectively. It should be noted that only one case of herpes zoster has been reported in placebo groups compared to two cases in intervention groups of the same study BREEZ1 with no statistically significant importance.

Nakagawa et al. (2020) noticed that a majority of reported AEs were not related to the study drug, with only five of the 23 reported AEs having been found to be related to the treatment; this is not significantly different from the placebo group. Another study done by Gooderham et al. (2020)[14] found a total of 184 of 267 patients (68.9%) experienced 402 TEAEs that were mostly mild; of these, 125 events reported by 64 of 267 (24.0%) patients were considered to be related to treatment, specifically abrocitinib and placebo. The most frequently reported of these are TEAE, and intestinal disorders were found to be significantly related to abrocitinib treatment. Only two out of seven reported serious adverse events in intervention groups were considered to be related to treatment.
Significant infectious AEs were only reported only in 10 cases out of a total of 1422 participants in all intervention groups of reporting studies, compared to zero out of 733 in placebo groups. Upper respiratory tract infection and gastrointestinal manifestations including diarrhea, nausea and headache were the most commonly reported treatment-emergent AEs by most of the included studies. The most commonly reported infections were upper respiratory tract infections or nasopharyngitis. The most commonly reported AEs that were related to the study drug was application site pain and infection. However, a meta-analysis of different secondary outcomes indicated that applying JAK inhibitors did not result in a statistically significant increased risk of AE compared to placebo groups.

Table4:-Summaryofsafetyoutcomes.

	TEAE		**Serious AE**		**AE-related withdrawal**		**Infectious AE**		**Significantly infectious AE**		**Malignancy**		**Death**	
Author (Year)	Placebo(n/N)	Interv. Groups (n/N)	Placebo (n/N)	Interv.Groups(n/N)	Placebo (n/N)	Interv.Groups(n/N)	Placebo(n/N)	Interv.Groups(n/N)	Placebo (n/N)	Interv.Groups(n/N)	Placebo(n/N)	Interv.Groups(n/N)	Placebo(n/N)	Interv.Groups(n/N)
Bissonnette (2016)	26/34	12/35	0/34	0/35	2/34	0/35	3/34	6/35	0/34	6/35	0	0	0	0
Bissonnette (2019)	7/9	20/27	0/9	0/27	0/9	2/27	0/9	0/27	0/9	0/27	0	0	0	0
Gooderham (2020)	32/56	187/211	2/56	7/211	9/56	36/211	13/56	89/211	0/56	1/211	0	0	0	0
Guttman-Yassky (2019)	24/49	44/75	0/49	1/75	5/49	6/75	6/49	16/75	0/49	0/75	0	0	0	0
Guttman-Yassky (2020)	25/40	94/126	1/40	3/126	3/40	10/126	8/40	57/126	0/40	3/126	0	0	0	0
Kim (2020)	17/52	59/203	0/52	1/203	1/52	1/203	5/52	9/203	0/52	0/203	0	0	0	0
Nakagawa (2018)	5/32	51/265	0/32	0/265	0/32	3/265	NR	NR	NR	NR	0	0	0	0
Nakagawa (2020)	6/52	23/106	0/52	0/106	0/52	0/106	NR	NR	NR	NR	0	0	0	0
Simpson BREEZE1 (2020)	135/249	213/375	6/249	3/375	4/249	4/375	53/249	100/375	0/249	0/375	0	0	0	0
Simpson BREEZE2 (2020)	137/244	203/370	9/244	13/370	2/244	12/370	72/244	97/370	0/244	0/370	0	0	0	0

NR : not reported

Figures 6–9 present the meta-analysis that compared the safety outcome of various placebos to that of JAK inhibitors.

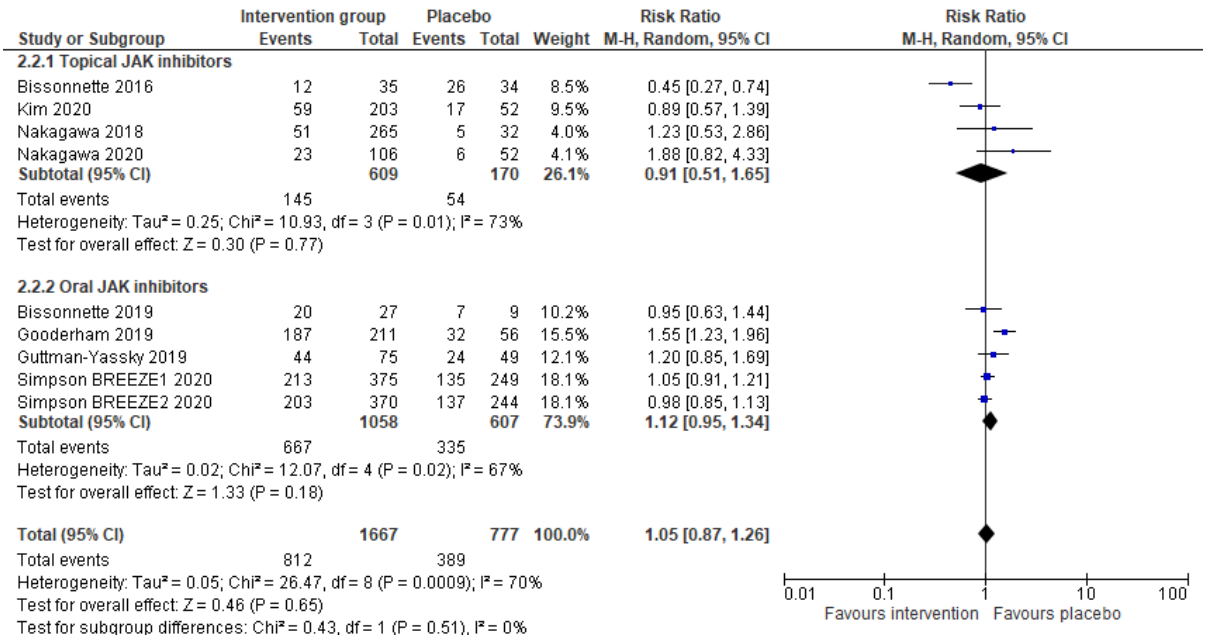


Figure6:- Meta-analysis comparing safety outcome of placebo to that of JAK inhibitors (TEAE).

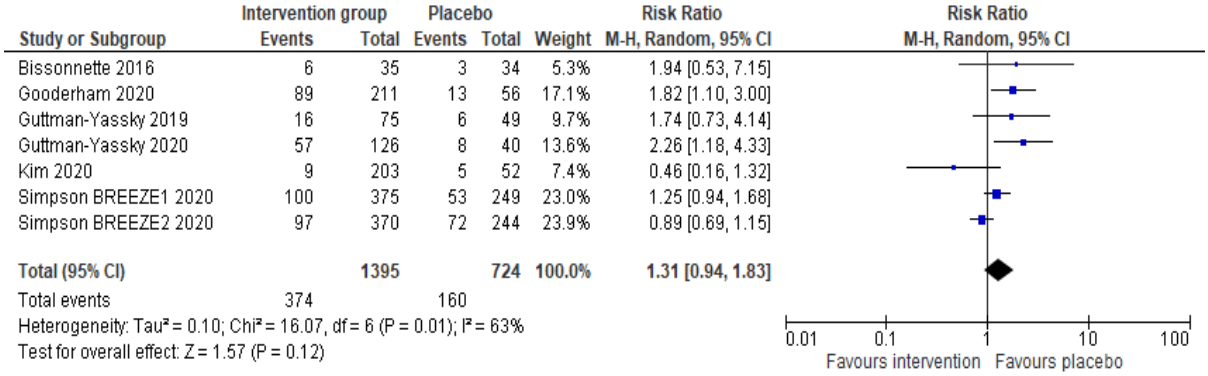


Figure7:- Meta-analysis comparing safety outcome of placebo to that of JAK inhibitors (infectiousAEs).

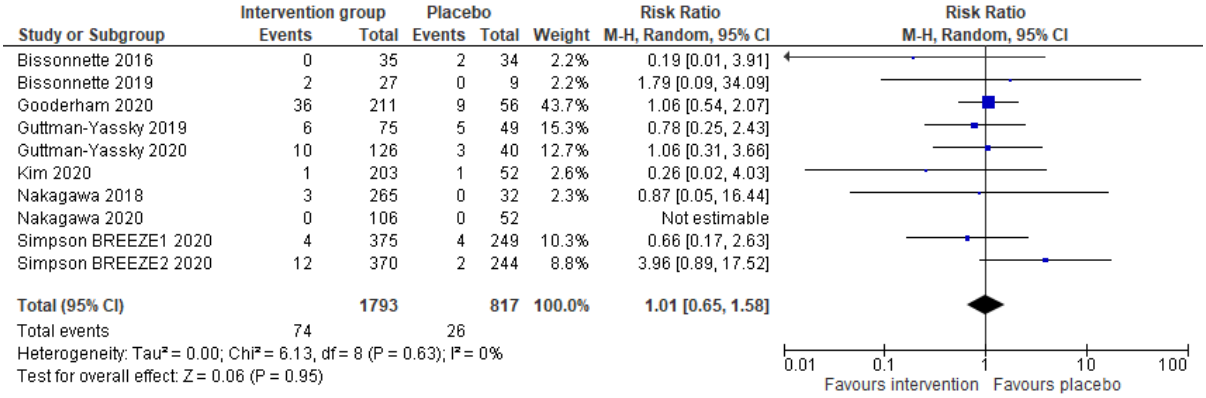


Figure8:- Meta-analysis comparing safety outcome of placebo to that of JAK inhibitors (AE-related withdrawal).

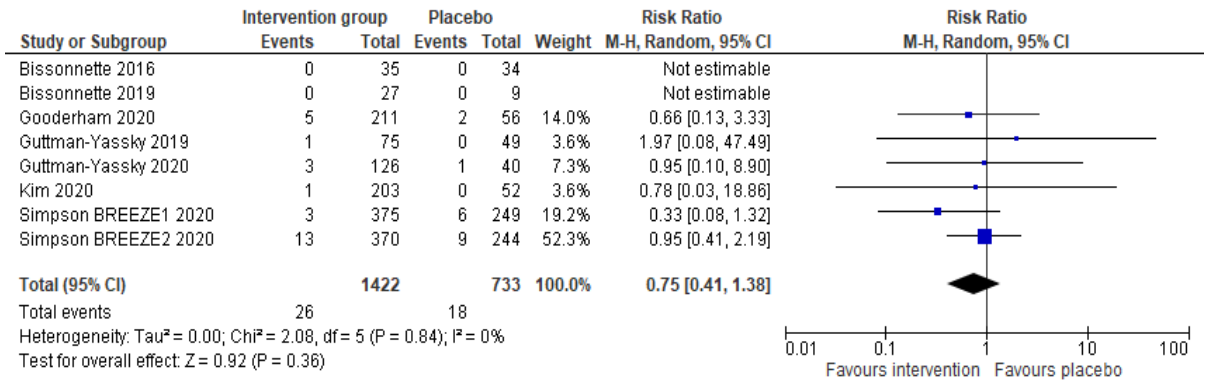


Figure9:- Meta-analysis comparing safety outcomes of placebo to those of JAK inhibitors (serious AEs)

JAK Selectivity and the Effect there of on Efficacy and Safety Outcomes

Non-selective JAK inhibitors showed significant clinical improvement and efficacy measured by EASI 50 with (Risk ratio = 3.37 [95%, CI 2.60–4.37], *P* = 0.95, n = 6 studies), compared to selective JAK1 inhibitor (RR 3.92 [95%, CI 0.66–23.44], *P* = 0.003, n = 2 studies) that showed insignificant statistical efficacy (see Figure 10). It is also important to note that JAK1 selective inhibitor showed an increased incidence of TEAE (RR 1.37 [95% CI 1.06–1.77], *P* = 0.14, n = 2 studies) (see Figure 11), compared to the statistically insignificant decrease in TEAE associated with treatment with non-selective JAK inhibitors (RR 0.98 [95% CI 0.83–1.15], *P* = 0.04, n = 8 studies). EASI 50 and TEAE were used to assess the effectiveness of JAK inhibitor selectivity on the efficacy and safety of the study drugs, as these two outcomes were measured by a large number of included studies and yielded high accuracy expectations

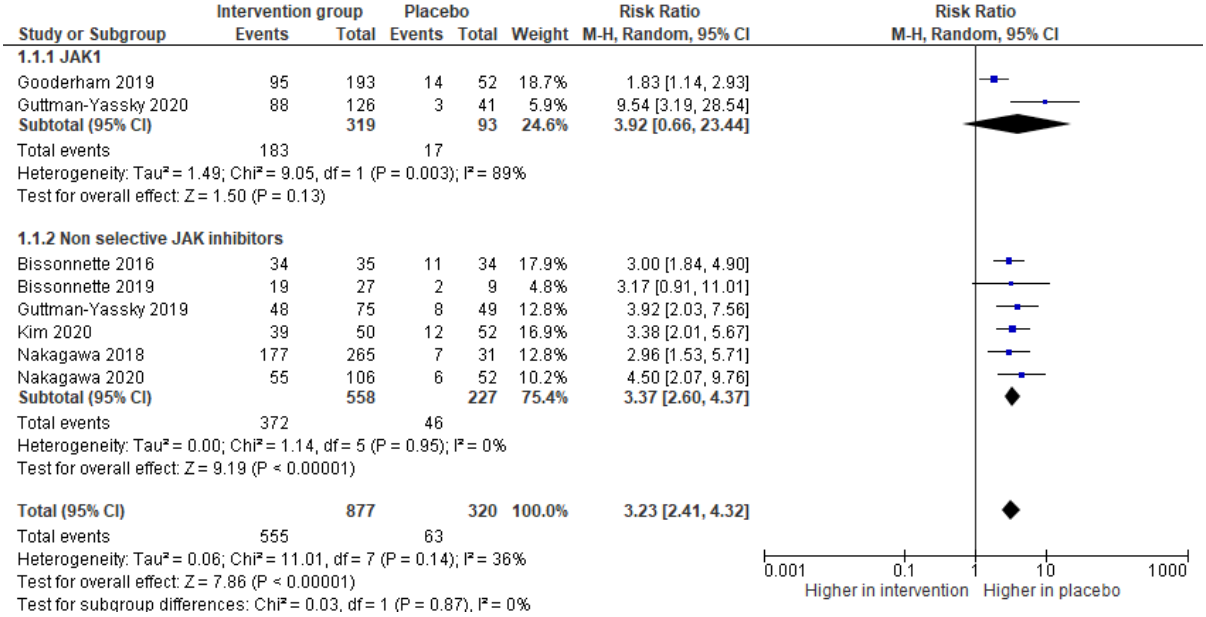


Figure10:- Efficacy outcome ofJAK1measured by EASI 50 compared to that of non-selective JAK inhibitors.

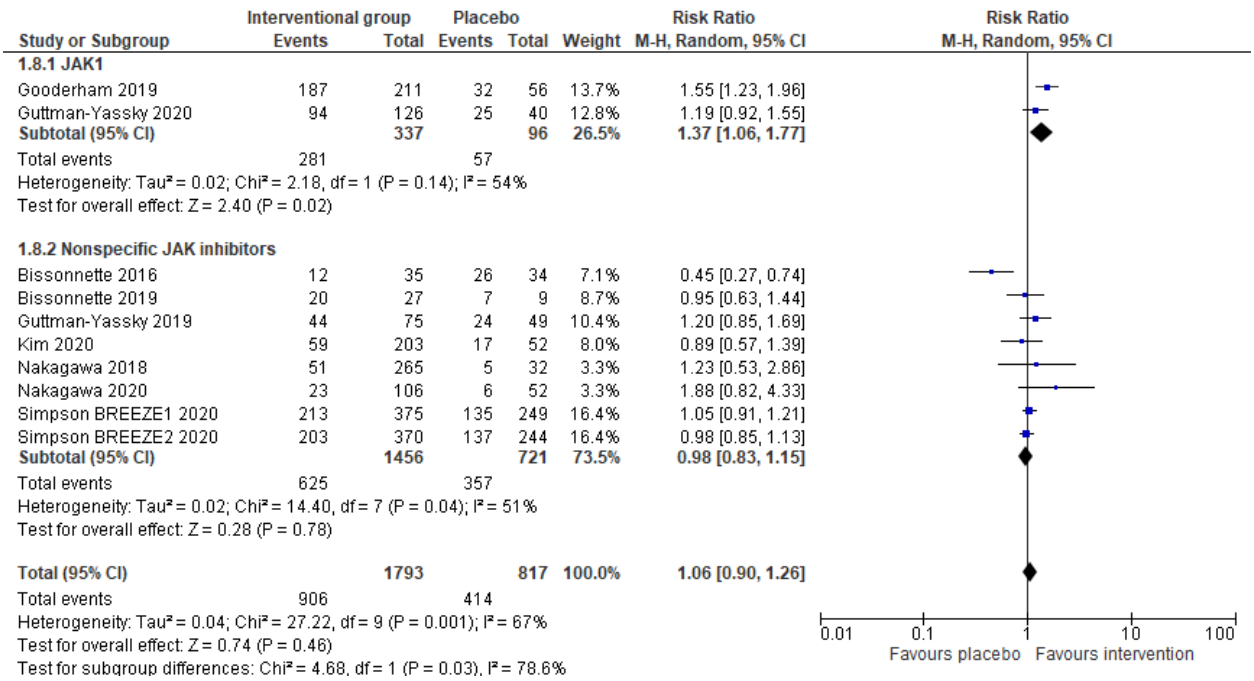


Figure11:- Safety outcome of JAK 1 measured by TEAE compared to that of non-selective JAK inhibitors

Discussion:-

AD is a disease that has a large burden; it affects physical, psychological, social and economic parameters.[21] Many drugs have been used to treat AD that mainly depend on emollients and topical anti-inflammatory medications; in most moderate and severe cases, however, these drugs are insufficient. [22] For such cases, systemic corticosteroids have become more effective, but safety factors cause their use to be restricted. [23] Other drugs, including systemic immunosuppressants, can be prescribed for AD, but these drugs are not approved in many countries and carry a high risk of side effects that minimize their application time. [22] One of the most recently approved treatment for moderate-to-severe AD is dupilumab. [24] This new drug has many issues related to its application and inadequate responses that vary across patients. As a result of all these factors, there is a need for alternative AD therapies. JAK inhibitors are orally and topically administered, and the small molecular size causes it to be eligible for consideration as a treatment for AD.

To my knowledge, this is the first systematic review and meta-analysis reporting on the efficacy and safety of JAK inhibitors in the treatment of AD. All randomized controlled trials of JAK inhibitors targeting adult patients with moderate-to-severe atopic dermatitis were included, and it was found that these JAK inhibitors are effective treatments for such patients. The pooled data also showed that intervention groups were not accompanied with significant increase in overall risk of adverse events or serious adverse events when compared to control groups. However, an increased risk of infection, mainly upper respiratory tract infections, was reported in most of the included RCTs but was not referred to in the study drug. In addition, gastrointestinal manifestations, application site pain and headaches were recognized as treatment-related AEs, although they were still not at a level of significance [14,15,17]

The patients that were evaluated in these trials demonstrated a clinically meaningful efficacy for the treatment. This has been detected through the increase in the proportion of patients achieving EASI-50 to reach 63.3% as shown by the pooled analysis. JAK inhibitor treatment was also associated with an almost three-fold increase in the chances for improvement of patients, as detected by achieving IGA 0–1,or two point improvement from the baseline and a 3.6-fold increase in the proportion of patients who achieved a four-or-more-point improvement below baseline in their Pruritus NRS score compared to the placebo groups. All these results were statistically significant.

Importantly, limitations of the included primary studies must be considered. Because the analysis was dependent on data that was exclusively retrieved from short-term trials, these trials ranged in duration from four weeks, as in the Bissonnette and Nakagawa trials,[12,13,18,19] to 16 weeks in the Guttman-Yassky and Simpson[16,20] to confirm these results, which are considered to be limited. It was also found that all the included trials described similar limitations

that can be resolved by including larger trials of longer duration and patient demographic characteristics in both adult and paediatric patients. The inclusion of active comparator and biomarker measures will aid in elucidating the relative efficacy, safety and mechanisms of action. [12]

It is also important to note that efficacy and safety outcomes reported by Nakagawa et al. (2020) in the second open-label 52-week extension part of their study confirmed that improvement in a modified EASI score was maintained and most adverse events were mild and unrelated to delgocitinib[19]; however, this part of the study was excluded from the analysis because of the absence of a comparator. Another limitation in the study is that there is a very limited number of studies assessing the efficacy and safety of the wide range of JAK inhibitors, which made it impossible to determine which JAK inhibitor could be more effective that the others or to even determine the best dosage for each drug. Anther limitation of the study is the differences within and between included primary studies that raised the heterogenicity of the data.

Drugs that inhibit cytokine signaling were found to be effective in improving AD. It was found that dupilumab suppresses both IL-4 and IL-13 signaling when is used in clinical settings.[24] Nemolizumab, which is an inhibitor of IL-31 signaling, was also of interest because of its antipruritic effect. [25] As with other cytokines, IL-4, IL-13 and IL-31 exert their biological effects via the JAK/STAT pathway. Clinical evidence show that these two drugs support the efficacy of JAK inhibitors, even though they vary in route of administration (systemic versus topical). Additionally, non-selective, pan-JAK inhibitors can broadly inhibit other cytokine signaling, which is considered to be a better profile compared to JAK1 inhibitors, given that many cytokines are involved in AD pathophysiology. This was confirmed by the results of the meta-analysis with statistically significant efficacy for the pooled-RR of pan-JAK inhibitors compared to no significant efficacy with selective JAK1 inhibitors (RR = 3.37 [95% CI 2.6–4.37] $P = 0.95$, $\chi^2 = 1.14$, $I^2 = 0\%$) and (RR = 3.92 [95% CI 0.66–23.44] $P = 0.003$, $\chi^2 = 9.04$, $I^2 = 89\%$), respectively.

All studies that moved from phase-2 to phase-3 showed similar results, which denotes that JAK inhibitors are considered to be a safe and effective treatment with no significant risk of AEs from their use.

Conclusion:-

In conclusion, this study showed that JAK inhibitors are effective novel medications with significant improvement of moderate-to-severe AD with overall tolerated safety in both the topical and oral forms. It is recommended that further studies with longer durations and larger sample sizes that cover a wider range of demographics are conducted

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Appendices:-

A. Appendix*1*

Joanna Briggs Institute for Meta-Analysis of Statistics Assessment and Review Instruments

1. JBI critical appraisal checklist for randomised control trials

Reviewer..... Date .....
Author..... Year .....

		Yes	No	Unclear	Not applicable
1	Was the assignment and treatment groups truly random?				
2	Were participants blind to treatment allocation?				
3	Was the allocation to treatment groups concealed from the allocator?				
4	Were the outcomes of people who withdrew described and included in the analysis?				
5	Were those assessing outcomes blind to the treatment allocation?				
6	Were the control and treatment groups comparable at entry?				
7	Were groups treated identically other than for the named interventions?				
8	Were outcomes measured in the same way for all groups?				
9	Were outcomes measured in a reliable way?				
10	Was appropriate statistical analysis used?				

Overall appraisal: Include ..... Exclude ..... Seek further info .....

Comments (include reasons for exclusion): .....

2. JBI critical appraisal checklist for non-randomized control trials

Reviewer..... Date .....
Author..... Year .....

1	Was study based on random or pseudo sample?				
2	Were the criteria for inclusion in the sample clearly defined?				
3	Were confounding factors identified and strategies to deal with them stated?				
4	Were outcomes assessed using objective criteria?				
5	If comparisons are being made, was there sufficient description of the groups?				
6	Was follow up carried out over a sufficient time period?				
7	Were the outcomes of people who withdrew described and included in the analysis?				

8	Were outcomes measured in a reliable way?				
9	Was appropriate statistical analysis used?				

Overall appraisal: Include ..... Exclude ..... Seek further info .....

Comments (include reasons for exclusion): .....

.....

.....

.....

B. *Appendix 2*

Data Extraction Form for Quantitative Research

Study Characteristics

1. Author: .....
2. Year of publication: .....
3. Journal: .....
4. Record number: .....

Study Method

1. Study Design:

RCT	Quasi-RCT	Longitudinal	Retrospective	Observational	Other

2. Purpose: .....

.....

3. Research Questions: .....

.....

Participant Characteristics

Country where the study was conducted	Setting	Population	Sex	Age	Sample size	Ethnicity (if applicable)	Socioeconomic status (if applicable)	Education level (if applicable)

Atopic dermatitis treatment Interventions

Strategy 1: .....

.....

Strategy 2: .....

.....

Outcome Measures

Outcome Description	Scale/measure

Study results

Dichotomous data

Outcome	Intervention ( ) number/ total number	Intervention ( ) number/ total number

Continuous data

Outcome	Intervention ( ) mean and SD (number)	Intervention ( ) mean and SD (number)

Authors' conclusions:

Comments: