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REVIEW OF BIOLOGICAL THERAPY FOR ATOPIC DERMATITIS

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ABSTRACT

Background: Atopic dermatitis, also known as 'atopic eczema', is considered to be common and recurrent skin disease which causes chronic inflammation prevalent at any age group in both adults and children in both the less-developed and the industrialized countries of the world. ***Objective:*** The aim of this systematic review was to derive authentic biological therapies for the accurate treatment of AD in current advanced medical era. ***Methods:*** We collected the clinical trials involved with the recent biologics for AD treatment through PRISMA exclusion criteria. Then we determined the safety and efficacy of these therapies by utilizing qualitative analysis and finally we determined risk of bias using Rev Man 5.4.1 tool for bias assessment. ***Results:*** The literature search yielded fifty studies for this review. Primarily all of the assessed interventions (molecular and biological treatments) showed significant superiority compared with placebo. Most of the biological agents showed significant improvement for participants with positive safety and efficacy levels except for Secukinumab and MOR106. When compared with placebo and other agents, biological agent's dupilumab and ustekinumab are the best choices for attaining safe levels of treatment. ***Conclusion:*** Continual assessment of newly introduced treatments is crucial to find the most effective or personalized treatments for AD owing to its recurrent and heterogeneous nature.

KEYWORDS: Atopic dermatitis, Atopic Eczema, Biological therapy, Biological drugs, Immunotherapy, Systematic Review.

1. INTRODUCTION

1.1. Background

Atopic dermatitis, also known as 'atopic eczema', is considered to be common and recurrent skin disease which causes chronic inflammation prevalent at any age group in both adults and children in both the less-developed and the industrialized countries of the world (Montes-Torres, Llamas-Velasco, Pérez-Plaza, Solano-López, & Sánchez-Pérez, 2015) and significantly deteriorates the quality of life in these patients, negatively affecting the society and economics as a whole (Barbarot et al., 2018). The frequency of AD among children can vary between 7 – 30% and in adults, 1 – 10% (Ibler & Jemec, 2015). Clinicians are able to provide temporary relief to the patients from the signs and symptoms, but the disease has not been curedcompletely yet. After treatments, patients suffer from numerous outbreaks (Bhatia et al., 2020). Usual topical calcineurin inhibitors and topical corticosteroids have been used for treating the patients with moderate to severe symptoms, however in order to achieve superior control, systematic treatment is necessary. The established alternatives for systematic treatment include azathioprine, methotrexate, cyclosporine and mycophenolate (Loizou et al., 2015). The variations in the inter- individual response have deemed necessary to investigate the secondary adverse effects of these drugs and look for new and improved ones that minimize these side effects and control the disease adequately. Further advancements can lead to other biological therapies or procedures that may serve as therapeutic alternative treatments vs. systemic treatments (El-Qutob, 2016). Recently there has been progress in the comprehension of the pathophysiology of atopic dermatitis and its multiple facets which can enable the discovery of novel substances useful in the systemic and topical treatment of AD. So, the new therapeutic procedures and strategies can bring about amazing advances in effective management of the conventional and refractory atopic dermatitis (Bhatia et al., 2020; Deleanu & Nedelea, 2019).

1.1.1. *History of Atopic dermatitis*

Atopic Dermatitis is not only a chronic inflammation, but also more expensive cutaneous disorder when compared to psoriasis and acne (Sacotte and Silverberg, 2018). The treatment of AD is based - on the pharmacological intervention by leukotriene receptor antagonists, calcineurin inhibitors, corticosteroids, and antihistamines (El-Qutob, 2016). While the clinical manifestations for the disease have variations according to the age of patient, the infant up to 2 years may experience erythematous papules and vesicles on neck, forehead, scalp and cheeks. The children with age more than 2

years up to puberty can present with extremely dry skin and lichenified papules and plaques in flexural areas of limbs (Nyankovskyy, Nyankovska, & Horodylovska, 2019). The symptoms in adults include eczema on neck, face, back, hands, toes, fingers, feet, upper arms and the flexural folds (Daltro, Meira, Santos, Ribeiro dos Santos, & Soares, 2020; Nutten, 2015). No matter what the age of patient is, the disease has deteriorating impact on the health and quality of life by heightening their financial costs, employment loss and sleep deprivation (Sacotte & Silverberg, 2018). Hence, the disease starts mostly in the first year of life and before the age of 5 years in more than 60 percent and 95 percent of the cases respectively (Eichenfield et al., 2014). In Latin America and Asia, nearly 20 percent of children are affected from the disease. Usually after childhood, the disease resolves on its own, but it may continue to adulthood in almost 10 – 30 percent of the cases (Daltro et al., 2020). Since atopic dermatitis is shown as xerotic skin and brings up acute flare-ups of intensely pruritic eczematous lesions in the patients (Deleanu & Nedelea, 2019; Dharmage et al., 2014). Some studies have reported that AD can persist in adulthood, for which the high risk factors include hand eczema and allergic rhinitis, however it shows variability in the patients. (Mortz, Andersen, Dellgren, Barington, & Bindslev-Jensen, 2015)

1.1.2. *Type of Atopic dermatitis*

There are two types of atopic dermatitis and each has its own characteristics, appearance and symptoms. Atopic dermatitis (AD) can be categorized into the extrinsic and intrinsic types. Some of its major features are mentioned below.

Extrinsic or allergic AD shows high total serum IgE levels and the presence of specific IgE for environmental and food allergens. The skin barrier is perturbed in the extrinsic. The extrinsic AD type (ADe) occurs in the majority of affected children and is associated with the presence of IgE against patient-specific patterns of inhalant and/or nutritive allergens (Ott et al., 2009).

Intrinsic non-allergic AD is the classical type with high prevalenceThe incidence of intrinsic AD is approximately 20% with female predominance. The clinical features of intrinsic AD include relative late onset, milder severity, and Dennie-Morgan folds, but no ichthyosis vulgris or palmar hyperlinearity. Intrinsic or non-allergic AD exhibits normal total IgE values and the absence of specific IgE. The skin barrier is not perturbed in the intrinsic type. The intrinsic type is immunologically characterized by the lower expression of interleukin (IL) -4, IL-5, and IL-13, and the higher expression of interferon-g. It is suggested that intrinsic AD patients are not sensitized with protein allergens, which induce Th2 responses, but with other antigens, and metals might be one of the candidates of such antigens (Tokura, 2010).

1.1.3. *Biologics for Atopic Dermatitis*

While the pathogenesis of this disease has primary associations with the abnormalities in T cell, specifically CD4+ T cells, these immune- pathogenic abnormalities play a critical role (Daltro et al., 2020). In this regard, T helper 2 (Th2) lymphocyte activation and the resultant released cytokines elevate the production of immunoglobulin E (IgE) that causes skin inflammation and also disrupts the skin barrier defect in atopic dermatitis patients (Klonowska, Gleń, Nowicki, & Trzeciak, 2018). The course of atopic dermatitis starts with biphasic inflammation, in which there is domination of Th2 profile and a cytokine storm, that includes a vast number of interleukin, such as IL-4, IL-13, IL-17, IL-22, IL-31 (Chaudhary et al., 2019). As a consequence, the immune signature gives rise to lesional and non-lesional skin. This shows that there has been a systemic switch to Th2 profile. In the case of chronic AD skin lesions, it has been shown that dominance of Th1/Th0 and production of interferon - gamma (IFN-γ) is increased, along with IL-6 and IL-12. The cytokines are, this way, produced from Th1, Th2 and Th17 cells, contributing to AD pathogenesis (Campione et al., 2020). Hence, the main factors for AD pathogeny include the Filaggrin gene mutation and biphasic pattern with T helper type 2 (Th2) and Th1 cells with chronic and acute phases of AD (Deleanu & Nedelea, 2019).

In the medical field, the biological therapies are majorly based on large protein molecules that are isolated from the micro-organisms or recombined with DNA technology which is expressed in microorganisms (Zugazagoitia, Molina-Pinelo, Lopez-Rios, & Paz-Ares, 2017). Different substances have been generated from the living organisms to treat the chronic disease that helps to suppress or stimulate the immune system to make the body fight against infection, cancer and other diseases (Deleanu & Nedelea, 2019). Well, molecular biological therapies are based on the molecular biological activity in or between cells, includingmolecular modification, synthesisand interactions. The(Di Marco et al., 2016).

Dupilumab, a biologic targeting IL-4 and IL-13, seems to correct both cutaneous and systemic abnormalities and has been approved for patients greater than or equal to 6 years old with moderate to severe AD. Biologics currently in trials for AD include those targeting IL-13, IL-31RA, TSLP, IL-33, OX40, and IL-22 (Boguniewicz, 2020).

2. METHODOLOGY

For the purpose of research, a systematic literature review was conducted to understand and investigate the various types, safety and efficiency of the biological therapies and possibilities involved in the novel clinical trials for AD patients having moderate to severe symptoms. The notable database, such as PubMed, Clinicaltrials.gov were thoroughly searched that pertain to the use of biological drugs in AD.

2.1. Inclusion and Exclusion Criteria

2.1.1. *Participants*

Studies were included if the participants were suffering from atopic dermatitis. Age, gender and specie was not a limitation for exclusion criteria. Included participants must have been suffering from atopic dermatitis. We considered trials that included adults with moderate-to-severe atopic dermatitis and who were at any stage of treatment.

2.1.2. *Intervention*

Studies were included that utilized biological therapies or drugs for atopic dermatitis treatment. This was to ensure the integrity of the intervention was maintained and that clear conclusions could be drawn about the efficacy of biological therapies. We considered trials that assessed systemic treatments, irrespective of the dose and duration of treatment, compared with placebo or with an active comparator.

2.1.3. *Study design*

Quantitative studies that were written in English were included. This included controlled studies, uncontrolled studies, single case series, and case studies. Qualitative studies were excluded. Previous systematic reviews, meta-analysis, or studies reporting previously published data were also excluded to avoid duplication of data. Studies that did not report relevant information to determine biological therapy effect on atopic dermatitis were also excluded. The key words included 'biological therapy', 'biological drug', 'immunotherapy', 'atopic dermatitis', 'atopic eczema', 'antibody treatment'. The list of articles generated were assessed on the basis of exclusion criteria, featuring only those articles which have been published in or after 2015 in English language and have mentioned or discussed biological therapy of AD in their title or abstract respectively. These drugs were listed in alphabetical order and their efficiency for AD was thoroughly analyzed. The references given in the articles retrieved from these databases were reviewed before the final selection.

2.2. Systematic Search Strategy

2.2.1. *Databases searched*

The following psychological, medical, and allied health professional databases PubMed and the Cochrane Library (Embase, CINAHL, and CT.gov. etc.) were searched. Science direct was also searched due to its generic database nature as a potential search ground.

- PubMed comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books (PubMed, 2020).
- CINAHL Plus is an electronic indexing database provided by EBOSCO Publishing. It searches literature related to nursing, allied health professionals, biomedicine and healthcare (CINAHL, 2020).
- Science direct is a freely accessible web search engine that indexes the full text or metadata of scholarly literature across disciplines and publishing formats. It includes most peer-reviewed online journals across Europe and America's largest scholarly publishers (ScienceDirect, 2020).
- The Cochrane Library is a collection of databases in medicine and other healthcare specialties provided by the Cochrane Collaboration. It hosts the collection of Cochrane Reviews, a database of systematic reviews and Meta-analysis which summaries and interpret the results of research. The library aims to make the results of well-conducted controlled trials available and is a key resource in evidence-based medicine (Cochrane Library, 2020).

2.3.2 *Search terms*

Articles were assessed and evaluated by combination of key words. The key words included 'biological therapy', 'biological drug', 'immunotherapy', 'atopic dermatitis', 'atopic eczema', 'antibody. No age filter was also applied. Clinical trials and trials filter was applied on PubMed and Cochrane library respectively. To ensure that the literature search was as comprehensive as possible a number of additional search strategies were used. The ancestry technique was applied to discover relevant articles from the reference lists of included studies based on the initial search.

2.3.3. *Initial study screening*

The titles and abstracts of the studies were scoped to decide whether they met the inclusion criteria. In cases where more numerical information was required the full text of the article was read. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was utilized for setting inclusion criteria (Appendix I) (Moher, Liberati, Tetzlaff, Altman, & Prisma, 2009) and PRISMA flow diagram was included. The PRISMA diagram outlines; identification, screening, inclusion and exclusion of all articles throughout the process with clarity.

2.3.4. *Data Extraction*

Information was extracted from the research articles in a systematic manner using a data extraction format. Data extraction was completed by the primary researcher and checked for completeness and accuracy by the secondary researcher. Disagreements where they occurred were resolved following discussions with supervisor/mentor.

2.3.5. *Unit of analysis*

The primary unit of analysis was the intervention. We did not work with studies with unclear and ambiguous methodological design that would incur data clustering. The trials with multiple intervention groups comparisons were treated as independent two-arm studies in the review. In this analysis, different comparisons were analyzed separately.

2.3.6. *Dealing with missing data*

We extracted, when possible, the intervention and its effect on atopic dermatitis for the outcome of study. Studies with missing data were excluded.

2.3.7. *Publication bias*

The publication bias was calculated for randomized clinical trials involving biological therapies for atopic dermatitis. Risk of Bias assessment and principle of summary measures were determined. The Cochrane Risk of Bias Assessment tool ((RevMan Version 5.4.1, 2020)) was used both for the safety studies, as well as efficacy studies (Higgins et al., 2011).

2.3.8. *Assessment of risk of bias in clinical trials in included studies*

We used Cochrane's 'Risk of bias' (RoB) tool to assess the risks of bias. Researcher independently assessed the risk of bias. According to the general principles in the *Cochrane Handbook for Systematic Reviews of Interventions*, the each following 'Risk of bias' domain was labelled as 'low', 'high', or 'unclear'.

•Selection bias (random sequence generation and allocation concealment items): The random method appropriate at low risk of bias if the allocation sequence was generated from a table of random numbers or was computer-generated. It was deemed inadequate or at high risk of bias if sequences could be related to endpoint. We stated it as unclear if the study mentioned that the trial was randomized, but did not explain how it was done.

Allocation concealment was considered proper if the trial stated that it was done via sequentially pre-numbered sealed opaque envelopes or by a centralized system. We considered a double-blinded study process as a low risk of bias.

• Performance and detection bias (blinding of participants and blinding of outcome assessor items): We evaluated the risk of bias separately for personnel and participants, outcomes assessors, and each outcome.

• Attrition bias (incomplete outcome data item): We checked if there was misrepresentation or missing samples in intervention groups, any measure taken to resolve missing data. We also checked for strategies to cope with missing data.

• Reporting bias (selective outcome reporting item): We checked if each outcome was estimated, analyzed, and reported. We compared outcomes mentioned in protocols and methodology with outcomes provided in the Results section. We assumed reporting bias inadequate if an outcome in the protocols was missing in the main report.

• Other risk of bias: We did not fulfil the 'Other risk of bias' item as we did not highlight particular circumstances leading to other risk of bias from particular trial designs, contamination between the experimental and control groups, and particular clinical settings.

Overall risk of bias

To evaluate the quality of our data and to interpret the systematic review bias, we used these six RoB criteria (random sequence generation, allocation concealment, blinding of participants blinding of outcome assessor, incomplete outcome data, and selective outcome reporting) in order to classify each trial (Higgins et al., 2011).

2.3.9. *Moderator variables*

A systematic review is designed to gain the effect of a given treatment on a specific sample from the population. In this research the effect of biological therapies on atopic dermatitis was investigated. The main reason of designing such research is inevitably to analyze studies that have a broad scope of methodologies. This results in introduction of a range of variables that can blur what the researcher is precisely looking for in the effect. These variables are labelled as moderator variables and can affect the strength and the direction of the analysis. Potential moderator variables include; EASI score, SCORAD, Clinical efficiency, percentage improvement from baseline and adverse effects for treatment safety and efficacy.

2.4. Summary of the chapter

This research is based on the inclusion- exclusion criteria for the identification of the biological therapy for AD. Moreover, the systematic literature review is used for analyzing the guidelines and tools that are used in the data selection. The clinical trials including the risks of the therapies and drugs are observed in this section for the efficient treatment of the disease.

3. LITERATURE REVIEW

3.1. Literature Search Outcome

The literature search was completed and yielded a preliminary database of 2788 articles from the electronic databases, primarily Science direct, PubMed and Cochrane Library (CINAHL, CT.gov, Embase, CTRP, PubMed). This initial pool of studies was reviewed (titles and abstracts) to determine eligibility. The full articles of potential studies were acquired and subjected to the inclusion and exclusion criteria resulting in a final group of studies.

PubMed

The database was searched for the three primary keywords shifting from general to specific criteria of our systematic review. The keyword search was also assisted by the Filter ***clinical and randomized control trials*** provided by the database. The Keywords generated 449 outputs, adding the keyword ***atopic dermatitis*** and ***atopic Eczema*** as primary keywords and ***immunotherapy, biological therapy*** and ***biological drugs*** as secondary keywords. The studies on the basis of year of publication were filtered from 2015-2020. Numerous medical databases exist nowadays, offering search facilities on clinical data. Among all databases PubMed can be accessed for free and its keyword search offers rapid update frequency. PubMed is considered a prime tool in biomedical electronic research (Falagas, Pitsouni, Malietzis, & Pappas, 2008).

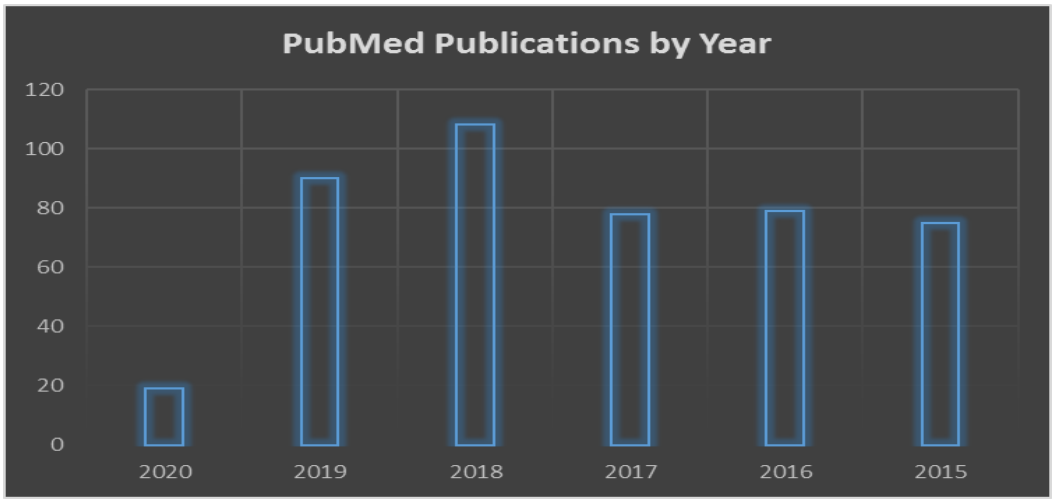

Figure 3.1. Publications in PubMed by year (2015-2020).

Cochrane library

Cochrane library is a diverse database for medical journals, maintain articles from various websites to aid researchers and medical personnel. The database was also subjected to similar keyword search employed for PubMed database. The keyword search was also assisted by the Filter ***trials*** provided by the database. The Keywords, atopic dermatitis generated 1695 outputs. The number of studies extracted from each respective origin database based on keyword search and filter are presented in Figure 3.2. The Cochrane Library contains high-quality, independent evidence to inform health care decision-making. The Cochrane Library contains several databases to aid medical research (Novak et al., 2010).

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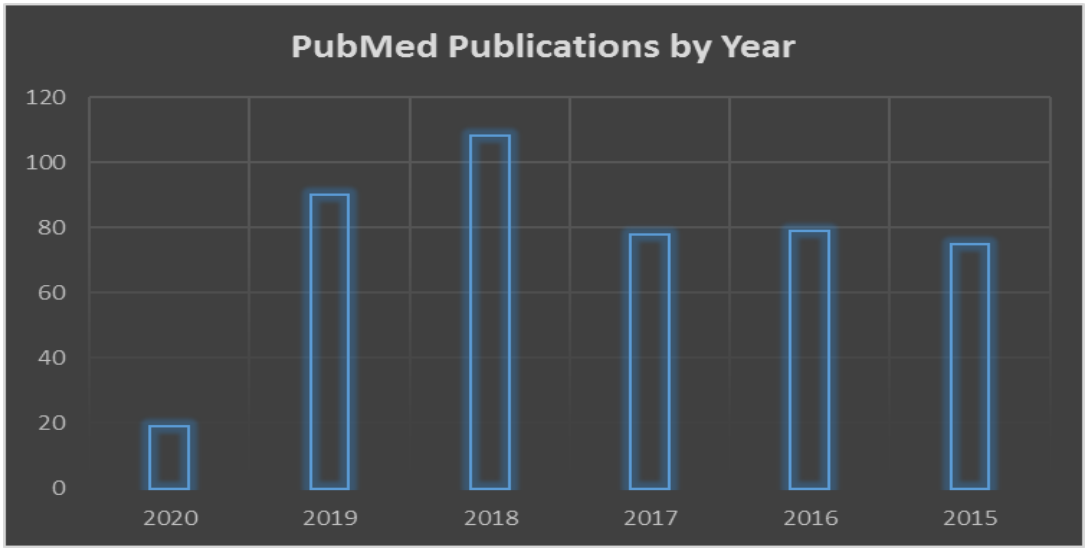

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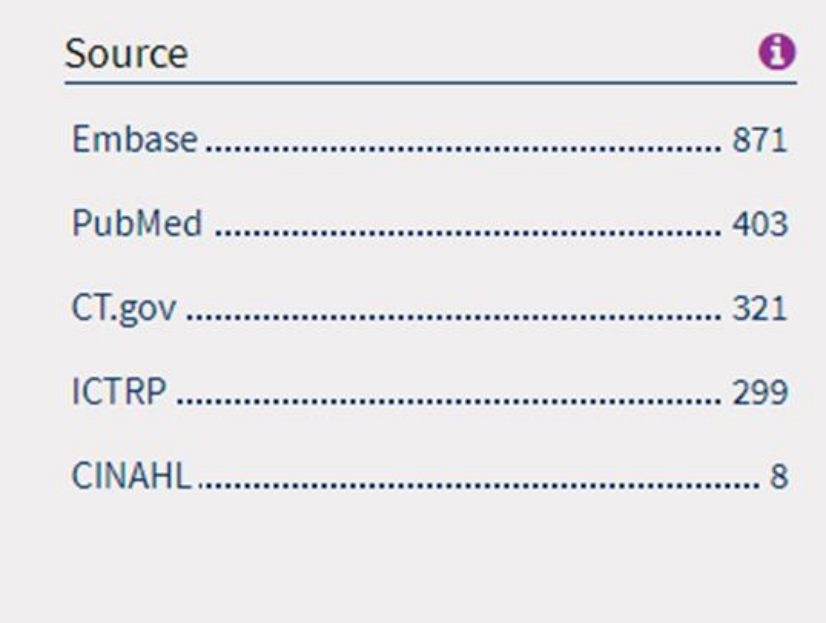

Figure 3.2. Number of publications in Cochrane Library by source from year 2015-2020.

3.3. Inclusion and exclusion of data

Study selection for the meta-analysis of safety and efficacy outcomes: Studies selected for safety reporting on molecular therapies were identified in accordance with PRISMA guidelines as summarized in the PRISMA Flow diagram (Moher, Altman, Liberati, & Tetzlaff, 2011). The PRISMA checklist is supplied as supplement in the Appendix I which was utilized to define the selection criteria for studies. The PRISMA-P checklist contains 27 numbered items that should be described, at minimum, in protocols of systematic reviews and meta-analyses (Tricco et al., 2018).

1695 and 1093 published studies were shown in Figure.3.3. 61 % studies were immediately excluded because of duplication and irrelevant presentation. The majority of articles were excluded during the initial screen including books, book chapters, theses and review articles. The remaining studies primarily gained from two databases PubMed and Cochrane library were filtered for criteriawith randomized clinical trials and general to specific key word search and resulted in 597 clinical trials. A number of articles were not intervention studies and some studies utilized samples that did not include atopic dermatitis. These studies were than manually assessed through title and abstract reading to separate the unwanted studies that don't match the objectives of this paper or contained missing data. Studies were not included the systematic review due to insufficient statistical information needed to assess outcome. The authors couldn't be contacted to obtain the necessary information. Thus, followed by the screening of the title and abstract, afterwards 97 studies were shortlisted and analyzed in full content analysis mode by the researcher to identify if they fulfilled required criteria. 47studies were later excluded owing to missing data and we selected fifty studies for this systematic review that suited our goals. Studies included in the systematic review are described in detail in Table 3.1.

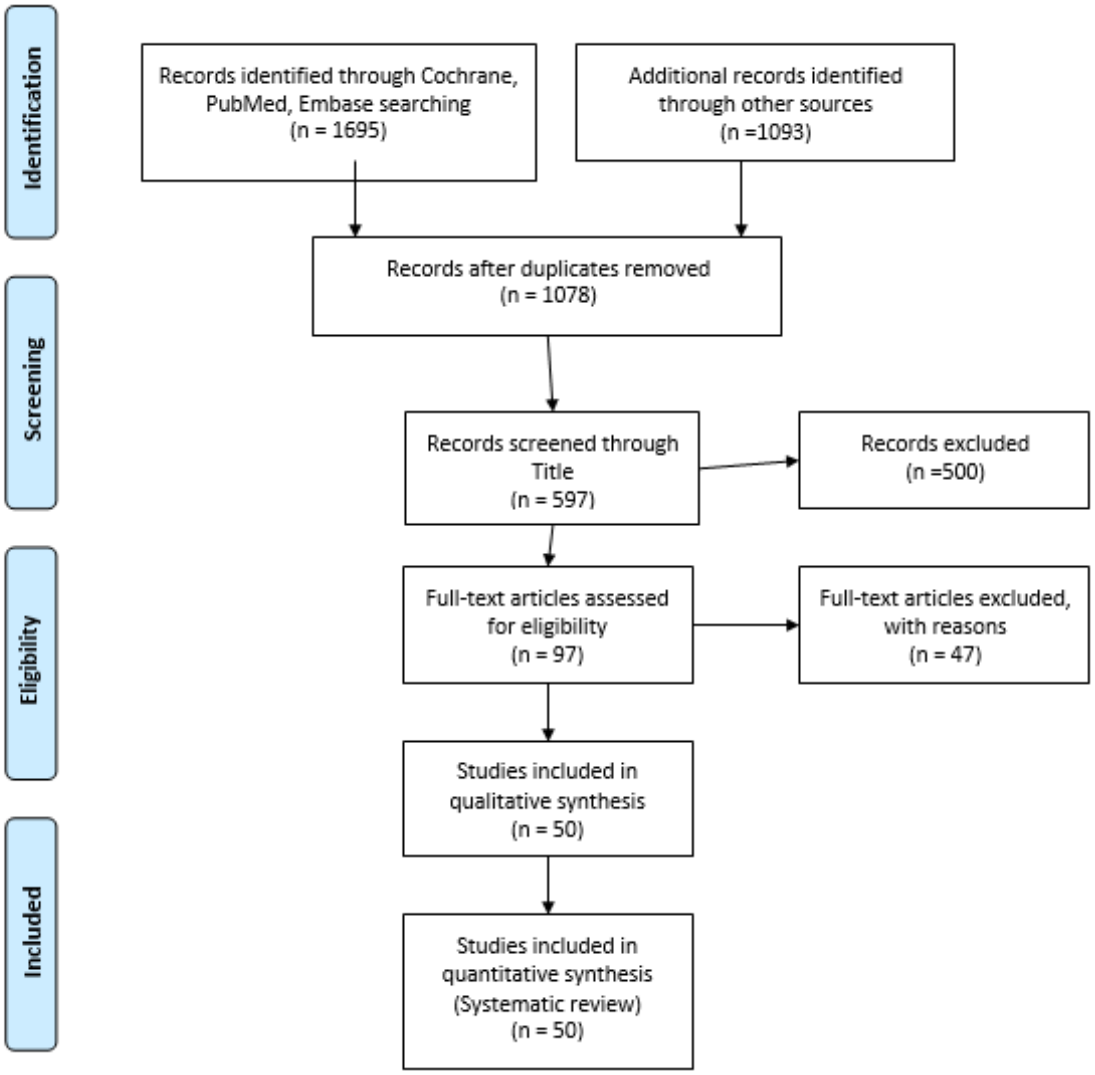

Figure 3.3. PRISMA Flowchart mapping out study inclusion-exclusion process.

3.4. Qualitative study assessment

After the application of inclusion criteria and screening studies with missing values we established fifty studies for qualitative assessment and systematic review. The descriptive parameters of the studies are presented in Table 4.1. All of the included studies were controlled studies, uncontrolled studies, single case series, and case studies. Sample type, Sample sizes, drugs, doses, evaluation period varied in each study. The sample groups were randomly selected in each study and did not affect the outcomes of the treatment. The studies evaluated the safety and efficacy of biological therapies against treatment of atopic dermatitis or atopic Eczema.

Table 3.1: Descriptive summary of studies included in Systematic review.

Author	Study type	Sample type	Sample size	Age (mean)	Condition	Treatment	Outcome measure	Efficacy	Safety (Adverse Effect)	Duration
(Jue & Jo, 2018)	Retrospective clinical study	Elderly patients	34	70.62 ± 5.39	Moderate to severe chronic Hand eczema	Alitretinoin	82.3% showed clinical improvement.	A safe and effective Treatment	Adverse events include headache, gastrointestinal symptoms, xerosis and dyslipidemia	147.85 days.
(Simpson et al., 2019)	Phase 2 Randomized Trial	Adults	185	38	Moderate to severe atopic dermatitis	Apremilast (APR30 and APR40)	A dose-response relationship was observed. APR40led to significant improvements	APR30 was safer but APR40was more efficient	Adverse events with APR30nausea, diarrhea, headache, and nasopharyngitis). With APR4 cellulitis	12 weeks
(Guttman-Yassky et al., 2018)	Random placebo controlled clinical trial		36		Moderate-to-Severe Atopic dermatitis	ASN002,	Best efficacy with ASN002 was seen with ≥79% improvements in mean EASI score	Showed improvements in clinical outcomes	No adverse effects reported	4 weeks
(Liew et al., 2020)	Phase 2 randomized clinical trial	Standard 4- or 6-mm biopsy specimens	10		Skin barrier defects in atopic Dermatitis	Belinostat		Belinostat is of clinical significance as a Candidate drug for AD treatment		
(Khattab, 2020)	Prospective, intra-patient, left-to-right, randomized, placebocontrolled study	Adults	26	37.8	Severe atopic dermatitis	Botulinum Toxin A	64.1 percent of patients reported an excellent response	Safe and effective therapy for atopic dermatitis of all grades	Not mentioned	Not mentioned
(Piscitelli et al., 2018)	Phase 1b study	Adults	8	28.5	Atopic dermatitis	Cerdulatinib (DMVT-502),	EASI scores improved from Baseline by 65% (P < 0.001).	Study provides proof of concept for the potential of topical Cerdulatinib as a treatment for AD	No safety-related Withdrawals.	14 days
(Purushothaman et al., 2018)	In vivo study	Balb/c mice			Atopic dermatitis	Compound 23 (catecholopyrimidine)	The dermatitis induced scratching frequency was significantly reduced in compound 23- (p < .01) treated	Compound 23 could be an effective PDE4 inhibitor for AD treatment	Not mentioned	

							AD-induced experimental mice			
(Bissonnette et al., 2018)	Intrapatient randomized trial	Adults	40	32.2	AD	Crisaborole	Crisaborole-treated lesions showed significant percentage improvement from baseline	Crisaborole showedimprovements in clinical efficacy measures	No serious AE was reported	43 days
(Wagner et al., 2017)	Uncontrolled, prospective pilot Study	Atopic dogs	18		Canine atopic dermatitis	Cytosine-phosphateguanine Oligodeoxyn-ucleotides	Mean improvements from baseline were 23 per cent and 44 per cent for Lesions and pruritus	Clinical improvement of canine AD with cpg GNP	Adverse event were Vomitus, diarrhoea, swelling of the popliteal lymph node and Swelling at the injection site	18 weeks
(Nakagawa et al., 2019)	Phase 2 clinical trial	Pediatric patients	103 (2 groups)	8.5	Atopic dermatitis	Delgocitinib	67.6% (EASI-50 And 50.0% EASI-75 scores	Improved clinical signs and symptoms in pediatric patients with AD	Adverse events were mild.	4 weeks
(Ariëns et al., 2020)	Long term cohort study	Adults	210	43.2	Treatment-refractory atopic dermatitis	Dupiluma	EASI-75 was achieved by 59.9% at week 16 and 70.3% at week 52.	Rapid improvement in clinical outcome measures.	Conjunctivitis	52-weeks
(Deleuran et al., 2020)	Phase 3 open-label extension study	Adult	1491	39	Moderate to Severe atopic dermatitis	Dupilumab	60 % patients receive EASIi-90.	The safety and efficacy profile supports dupilumab treatment for moderate to severe AD.	Nasopharyngitis, conjunctivitis, and injection-site reactions	
(Silverberg et al., 2020)	Retrospective cohort study	Adults	1963	42.1	Atopic dermatitis	Dupilumab	Dupilumab persistence (95% confidence interval) at 6 and 12 months was 91.9% and 77.3% respectively	Dupilumab persistence at 12 months was high, suggesting patient satisfaction with effectiveness	Not reported	12 months
(Alniemi & McGevna, 2019)	Single patient case study	Adult woman	1	49	Atopic Dermatitis, alopecia areata.	Dupilumab	Significant improvement of Cutaneous disease and quality of life. Minor flares, with a BSA of less than 5%	Dupilumab Reported to be effective in a patient with atopic dermatitis and concomitant alopecia areata.	No adverse clinical symptoms .	8 months

(Li et al., 2020)	Single patient case study	Adult Man	1	50	Atopic dermatitis	Dupilumab		A novel association between dupilumab use and corneal ulceration.	Corneal ulceration	3 weeks
(Cork et al., 2017)	Open-label phase iia trial	Peadritics	Adolescents (12 to < 18 years) with moderate-to-severe AD and children (6 to < 12 years) with severe AD			Dupilumab	EASI significantly improved by 66.4% and 69.7%	The efficacy and safety with the significant clinical benefit for AD in children	Most adverse Events were mild. nasopharyngitis	12 weeks
(Callewaert et al., 2020)	Double-blind, placebo-controlled study		54		Moderate to severe AD	Dupilumab	During dupilumab treatment, microbial diversity increased and the abundance of S. Aureus decreased.	We conclude that clinical improvement of AD correlated with increased microbial diversity and reduced abundance of S. Aureus.	Not reported	16 weeks
(Schneeweiss et al., 2020)	A propensity score-matched cohort study		1,775		AD	Dupilumab	The 6-month risk for any conjunctivitis was 6.5% in dupilumab. The risk of 66 serious infection was 0.6% in dupilumab	Dupilumab shows a low risk of serious infections and is associated with a clinically meaningful increase in conjunctivitis	Conjunctivitis	6 months
(Jo et al., 2020)	Canadian retrospective study		30		Moderate-to-severe atopic dermatitis	Dupilumab	67% patients reached efficacy endpoint	Higher efficacy profile for dupilumab with no new safety concerns	Conjunctivitis, Herpes infection and injection site reaction	16 weeks
(Strowd & Feldman, 2017)	The randomised, placebocontrolled, Double-blind study		740		Atopic dermatitis	Dupilumab	EASI-75 was achieved by 64%, 65% and 22% in three dose group	For patients with extensive resistant disease, dupilumab is likely to be the first biologics that may offer safe and effective control of the disease	Non-infectious conjunctivitis	52 weeks
(Armario-Hita et al., 2019)	Realtime clinical practice study	Adult	27		Moderate to severe atopic dermatitis	Dupilumab	Baseline SCORAD of this series was 58.7, while pruritus VAS was 8.18	In our series, dupilumab improved significantly the signs and symptoms of AD	Mild conjunctivitis	12 weeks

(Faiz et al., 2019)	a real-life French multicenter adult cohort	Adult	241		Atopic dermatitis	dupilumab	A ≥75% improvement in SCORAD was achieved in 16.6% patients, and a ≥75% improvement in EASI was achieved in 48.8% patients	This study demonstrated dupilumab effectiveness but it also revealed a higher frequency of conjunctivitis and eosinophilia. .	Conjunctivitis, Eosinophilia	4 months
(Ariens et al., 2018)	Clinical trial		156		Moderate to severe AD	Dupilumab vs. Ciclosporin	EASI 50 responders to dupilumab vs. Ciclosporin treatment were 93% vs. 77%. For EASI 75, 81% vs. 56%	Higher relative efficacy of dupilumab compared with ciclosporin	Not mentioned	30 weeks
(Chen et al., 2019)	Proof-of-concept first-in-class phase 2a study clinical trial	Adults	12		Moderate to severe atopic dermatitis	Etokimab	83% achieving EASI-50 and 33% EASI-75	Human in vivo findings confirm an IL-33 Upstream role in modulating skin inflammatory cascade	Etokimab was generally well tolerated with no known direct side effects	A single systemic administration
(Guttman-yassky et al., 2018)	Randomized, double-blind, placebocontrolled, repeated-dose study		62		Atopic dermatitis	GBR 830	EASI 50 achieved by 76.9% patients	Treatment with GBR 830 resulted in reductions in both the acute and chronic stages of AD	Safe and well tolerated	71 days
(Zolkipli et al., 2015)	Prospective, randomized, double-blind, Placebo-controlled, proof-of-concept study	Infants	111	Less than 1 year old	High risk of atopy	High-dose house dust mite (HDM) allergen	Significant (P 5 .03) reduction in Sensitization to any common allergen (16.0%) .	HDM oral immunotherapy is well Tolerated in children at high heredity risk.	No adverse events	12 months
(Kasrae et al., 2015)	Randomized clinical trial	Infants	100	Less than 20 months	Mild to moderate Atopic eczema	Human breast milk HBM versus Hydrocortisone 1% ointment	No significant differences between these two groups With same effects	The same results in the healing of AD, HBM can be used because of low cost and accessibility	Breast milk had no side effects	21 days
(Park et al., 2020)	In vivo analysis	Mice			AD	I. Inflexus (Thunb.) Kudo extract (IIE)	Topical Application of IIE reversed the effects of AD on scratching behavior, ear swelling, open-field Locomotion, sucrose preference, and levels of ige,	IIE is a candidate anti-AD therapy due to its ability to exert neuro-protective and Anti-depressant effects	Not reported	

							histamine, corticosterone, serotonin, and Inflammatory markers			
(Nakagawa et al., 2020)	Phase 1, single-center, open-label, repeated-dose study,	Japanese Patients	22	33.6	Moderate to severe AD	KHK4083	The EASI score decreased to 24.50	Repeated intravenous infusion of KHK4083 had an acceptable safety profile in patients with Moderate to severe AD	There were no deaths, serious adverse events or discontinuations	155 days
(Simpson et al., 2018)	Randomized,placebo-controlledphaseiitrial(T	Adults	209		Moderate-to-severe atopicdermatitis	Lebrikizumab	82.4 % patients achieveEASI-50 with lebrikizumab 125 mg every 4 week.	Lebrikizumab 125 mg led to a significant improvement and was well tolerated in patients with moderate-to-severe AD.	Adverse events were mild or moderate	12 weeks
(Kim et al., 2017)	Phase I/iia Studies	Adult	34	20-60 years old	Moderate-To-Severe Atopic Dermatitis	Mesenchymal stem cells (mscs)	Fifty-five percent of Patients in high dose hucb-MSC-treated group showed a 50% reduction in The EASI	Infusion of hucb-mscs might be an effective Therapy for patients with moderate-to-severe AD.	No serious adverse events occurred	3 months
(Goujon et al., 2018)	Phase III Randomized Noninferiority Trial	Adults	97		Moderate-to-Severe Atopic Dermatitis	Methotrexate Versus Cyclosporine	Methotrexate was inferior to Cyclosporine. SCORAD 50 was 8% in the methotrexate arm versus 42% in the cyclosporine arm	Methotrexate was inferior to Cyclosporine	The treatment related adverse events were more frequent with cyclosporine	8 weeks
(Thaci et al., 2018)	Phase I study		56		Moderate to severe AD	MOR106	The study was not statistically powered to show differences in efficacy between treatment groups	No significant effect	no serious adverse events reported	4 weeks
(Nagula & Wairkar, 2020)	In vitro and in vivo investigation	Male Albino Wistar rats	30	2-3 months		Naringenin	Total white blood cell count serves as Marker for treatment. Reduction in WBC count was observed 20.6 ± 6.3109/L	Can be further explored as natural remedy for atopic dermatitis	Safe for use and well tolerated	48 hours

(Silverberg, Pinter, et al., 2020)	Phase 2B randomized study	Adults	226		Moderate to severe AD	Nemolizumab	Nemolizumab improved EASI, IGA, and/or NRS-itchscores, with the 30-mg dose	Nemolizumab resulted in rapid and sustains improvements in cutaneous signs of inflammation and pruritusin patients with AD	Nasopharyngitis and upper respiratorytract infection.	24 weeks
(Maeda-Chubachi et al., 2018)	Phase 1b, multi-center, Randomized, double-blind, Vehicle-controlled Study	Adult men	48		Mild-to-Moderate Atopic dermatitis	Nitric oxide-releasing Cream SB414	18% achieved EASI-50 In the SB414 2% group	Demonstrated trends suggestive of efficacy. Lower dose had a more favorable tolerability profile	Application Site reactions	2 weeks.
(Marsella & Ahrens, 2018)	A randomized placebo pilot study	Atopic beagle dogs	10		Atopic dermatitis	Oclacitinib	Oclacitinib significantly increased (P = 0.006) time to develop skin reactions compared to placebo	Oclacitinib delayed development of dermatitis at the site of Allergen application	Not mentioned	4 weeks
(Price et al., 2019)	Randomized placebo controlled trial	Adults	16		Moderate-to-severe AD	Prednisolone	Significantly Improved EASI, SCORAD, IGA, and POEM scores ($p<0.05$)	Prednisolone improved clinical responses in adults With moderate-to-severe AD	Not mentioned	14 days
(Chen et al., 2020)	In vivo and vitro lab study	Male BALB/c mice			Atopic dermatitis	Pseudoephedrine	PSE suppressed Serum TNF-α and ige levels, reducing cytokines (IL-1β, IL-4, IL-6, IL-13, IL-33, TSLP, and IL-23) and neutrophil Migration factors (CCL2 and MMP-9) in skin tissues	PSE could inhibit inflammatory responses in atopic dermatitis	Not reported	2 weeks
(Myles et al., 2018)	Open-label phase I/II safety and activity trial	10 adult and 5 pediatric patients	15		Atopic dermatitis	R. Mucosa therapy	Treatment with R. Mucosa was associated with significant decreases in measures of disease Severity, topical steroid requirement, and S. Aureus burden.	These early results support continued evaluation of R. Mucosa therapy with a placebo-controlled trial.	There were no adverse events or Treatment complications.	12 months
(Ungar et al.,	Phase 2 randomized	Adults	41 patients		Atopic dermatitis	Secukinumab		Minimal changes in the	Orbital cellulitis,	16 Weeks

2020)	clinical trial		26 patients with extrinsic AD and 15 With intrinsic AD were enrolled.				Secukinumab-treated patients showed no significant improvement	Lesional profiles of the secukinumab-treated groups	upper Respiratory infection, and streptococcal pharyngitis	
(DeBoer et al., 2016)	Clinical study	Atopic dogs	10		Spontaneous AD.	Sublingual Immunotherapy (SLIT)	Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03 scores declined from 76.5 to 59	SLIT treatment produced clinical improvement in dogs with dust mite associated AD		6 months
(Chan et al., 2019)	Prospective case-controlled study	Children	120	14.3	Atopic dermatitis	Sublingual Immunotherapy	The total symptom scores decreased from 46.40 to 29.38 (p = 0.0004)	Expensive than conventional treatments but beneficial for atopic dermatitis and comorbid allergic conditions	Mild local sublingual or throat itchiness	12 months
(Liu et al., 2019)	Multi-centre, Randomized, double-blind, placebo-controlled Study	Adults	239	31	Atopic dermatitis	Sublingual immunotherapy	Clinical efficacy rate in high and medium dose treatment reached to 56.00 and 58 %respectively.	Beneficial effect of SLIT with high or medium dose on AD	Adverse events are slight, and no life-threatening reaction	36 weeks
(Wollenberg et al., 2019)	Phase 2b study	Adults	204		Moderate to severe AD	Tralokinumab,	Significantly improved change from baseline in Eczema Area Severity Index score	Tralokinumab treatment was associated with early and sustained improvements in AD	Upper respiratory tract infection	12 weeks
(Guttman-Yassky et al., 2020)	Randomized placebo controlled clinical trial	Adults	167	39.9	Moderate to severe atopic dermatitis	Upadacitinib	EASI 50, EASI 75, and EASI 90 responses was also achieved at week 16; EASI 100 was achieved by 2.4% patients	A dose-response relationship was observed for Upadacitinib efficacy; the 30-mg once-daily dose showed the greatest clinical benefit	Infections were more common with upadacitinib	16 weeks
(De Bruin-Weller et al., 2018)	Phase iib randomized, placebo-controlled trial				Moderate to severe AD	Upadacitinib	Percentage improvement in EASI, was met in the 7.5, 15 and 30-mg upadacitinib groups	Upadacitinib treatment showed a positive benefit	Upper respiratory tract infection	88 weeks

							by 39%, 62% and 74% of patients			
(Khattri et al., 2017)	Phase 2 randomized clinical trial			40	Atopic dermatitis	Ustekinumab	Significant improvement in symptoms (P value 0.05)	Safe treatment but unclear performance	Not reported	
(Lee et al., 2018)	In vivo lab study	Hairless mice	7 week old		Atopic dermatitis	PAC-14028	Improved AD-like dermatitis and skin barrier functions, and restored the expression of epidermal differentiation markers.	PAC-14028 showed potential towards AD treatment	Not mentioned	11 days

AD
atopic dermatitis
AE
adverse event
DLQI
Dermatology Life Quality Index
EASI
Eczema Area and Severity Index
EASI50
EASI score improvement of at least 50%
EASI75EASI score improvement of at least 75%
IQR
interquartile range
SCORAD
Scoring Atopic Dermatitis
SCORAD50
SCORAD score improvement of at least 50%
SCORAD75
SCORAD score improvement of at least 75%

3.5. Introduction to Atopic dermatitis and biological therapy

Atopic dermatitis (AD) is a widespread skin ailment with a permanent prevalence of 20%, and the higher percentage of patients are children. As time moves on, more developments have been witnessed in regard to figuring out the pathophysiology of this disease process and creating more personalized therapies (Kennedy et al., 2018).

Severity of disease, age level, and presence of associated persistent diseases were discovered as contributors of prolonged AD persistence. AD can be impacted by climate and other environmental factors. Seasonal and other natural factors can cause AD patients to experience flare episodes that subsides in the absence of triggers. AD patients have variable responses to emollients and prescription topical therapy, which complicates the permanent control of AD signs and symptoms (Lee et al., 2020).

Atopic dermatitis is a chronic, relapsing, non-contiguous, exudative eczema/dermatitis, which demonstrates complicated attributes with multiple related conditions owing to the disruption the stratum corneum barrier. This consequently manifests as disturbed skin function and an increase in trans-epidermal water loss (TEWL), which eventually causes dehydration, and after a list of inflammatory events characterized by the production and release of several cytokines, chemokines and interleukins AD is formed (Damiani et al., 2019).

AD is divided into extrinsic and intrinsic categories based on the presence or absence of allergen-specific IgE antibodies. Extrinsic or allergic AD is identified by high total serum IgE levels, as these IgE being specific for environmental and food allergens generates allergic bronchial asthma or allergic rhinoconjunctivitis in 70–80 % of AD patients. While, intrinsic or non-allergic AD is characterized by normal IgE levels and the absence of specific IgEs; it does not elevate respiratory problems, and patients expresses a void skin-prick test response to routine aeroallergens or food allergens. However, the clinical symptoms that exhibit the severity of both AD types are not highly different in children and adults (Yan et al., 2020). Development of AD may also be induced by microbiome formulation during infancy, with commensal staphylococci having a protective effect and being significantly less abundant in children who go on to develop AD by 12 months. Presently S. aureus remains the dominant organism in terms of potential contribution to AD pathogenesis (Harkins et al., 2019).

3.5. Biologics used in the biological therapy for the treatment of Atopic dermatitis

Atopic dermatitis treatment works towards symptoms management and maintenance of long-term AD control. These therapeutic management systems need to be patient centric and should include elimination of specific trigger factors, skin barrier rehabilitation using moisturizer, and a step-up and step-down technique targeted at lowering inflammation based on severity of the disease. The selection of anti-inflammatory therapy is mainly dependent on disease severity. Such as mild atopic dermatitis can normally be managed with topical treatments, while more severe disease might require phototherapy, systemic immunomodulatory therapy, or both (Harper & Oranje, 2019).

As AD treatment has begun to expand forward in the dimension of medicine specificity, numerous biologics and small molecule agents have been created to block specific cytokines, cytokine receptors, or transcription factors. Dupilumab a monoclonal antibody is a prime example that reduces type 2 inflammation by antagonizing IL-4 and IL-13 action and has been cleared by the US Food and Drug Administration for patients with moderate-to-severe AD (Ahn et al., 2020). Dupilumab, also blocks the key drivers often associated as comorbidities, thus inhibiting their signaling (Deleuran et al., 2020). Delgocitinib has inhibitory effects on all types of JAK family kinases (JAK1, JAK2, JAK3, and tyrosine kinase. Topical delgocitinib (JTE-052), a novel Janus kinase inhibitor, had been known to be clinically beneficial in adults with atopic dermatitis (AD). However, the efficacy of topical delgocitinib in pediatric patients with AD is under scrutiny (Nakagawa et al., 2019).

Preclinical research shows that disruption of JAK1 signaling lowers itch severity by process including TH2 cytokines, which may further activate neurons to elicit itching and supports a potential role for JAK inhibitors in the treatment of AD. Upadacitinib is an oral reversible JAK1 inhibitor engineered for increased selectivity for JAK1 over JAK2, JAK3, and tyrosine kinase 2 and is currently being investigated for several immune-mediated inflammatory diseases. (Guttman-Yassky et al., 2020).

3.6. Clinical Trials of Different Biologics in the Treatment of Atopic dermatitis

Although various severity scales, such as the Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure, Severity Scoring of Atopic Dermatitis, and others, have been validated, they are not routinely used in current clinical practice. Questions directed toward the patient should provide insight into disease severity on a case-by-case basis. The severity of itch the patient experiences, the impact the disease has on sleep patterns and daily activities, and disease persistence should all be taken into account during evaluation (Aldredge, 2020).

Various clinical studies have been included in our systematic review targeted at exploring safety and efficacy of various new emerging therapies. The first study by used towards elderly patients in treating hand eczema and reported positive outcomes in more than 80 percent patients. Although it was followed by adverse

effects in patients. Adverse events were found in 29.4% participants comprising of headache, gastrointestinal symptoms followed by xerosis dyslipidemia occurred or worsened in patients. But overall Alitretinoin can be considered a safe and effective treatment option in elderly patient with moderate to severe hand eczema (Jue & Jo, 2018). In another study a dose-response relationship was studied for two doses of Apremilast (APR30 and APR40)APR40 was found more efficient in treatment but in terms of safety APR30 was largely consistent with common known adverse effect profile while APR40 showed more intense AE (Simpson et al., 2019). Another novel treatment was tested on AD patients through ASN002 administration, and was well-tolerated and exhibited significant and positive outcomes through EASI scores while no adverse effects were reported (Guttman-Yassky et al., 2018). Belinostat has also been tested recently as a novel therapy for AD and has been discovered as a potential candidate drug for AD treatment and eliminating spread of this disease (Liew et al., 2020).

Severe AD is an even bigger concern when designing trials for competitive drugs. Botulinum Toxin A has shown suitability towards AD patients suffering from severe conditions with no known AE. However since the sample population is low as 26, more study is needed towards exploring its safety (Khattab, 2020). Proof of concept studies have been done on Cerdulatinib (DMVT-502) (Piscitelli et al., 2018) and Compound 23 (catecholopyrimidine) (Purushothaman et al., 2018) via phase one and in vivo lab studies on mice and they have exhibited clinically efficient outputs in diminishing AD like symptoms with no known AE so far. Crisaborole also reversed biomarker profiles of skin inflammation and barrier function, with associated improvements in clinical efficacy measures, highlighting the therapeutic utility of this drug in patients with AD. Adverse effects were associated but weren't labelled serious by the study (Bissonnette et al., 2018).

Cytosine-phosphateguanine Oligodeoxynucleotides had shown a clinical improvement of canine AD comparable to allergen immunotherapy but fifty percent dogs experienced at least one adverse event. These included vomitus, diarrhoea, swelling of the popliteal lymph node and swelling at the injection site (Wagner et al., 2017). In a phase 2 clinical study Japanese patients aged 2 through 15 years with AD received delgocitinib ointment daily for 4 weeks. At the end of treatment (EOT), Eczema Area and Severity Index scores in delgocitinib groups were significantly reduced. Similarly, all other efficacy parameters, including Investigator's Global Assessment and pruritus scores, significantly improved. Adverse events were mild. These study results indicated that delgocitinib ointment can be a promising therapeutic option for pediatric patients with AD (Nakagawa et al., 2019).

Dupilumab has been one of the most explored drugs to date in modern therapies towards atopic eczema. Several studies conducted from the year of 2015-2020 and included in our review provided evidence of its efficiency and its AE. Long term treatment with dupilumab has resulted in a rapid improvement in clinical outcome measures, and have been found to further improve during the 52-week follow-up period (Ariëns et al., 2020). The ongoing, multicenter, open-label extension study evaluated long-term dupilumab treatment in adults for AD. This analysis examined patients given 300 mg dupilumab weekly for up to 76 weeks. The safety profile was consistent with previously reported trials and adverse events included nasopharyngitis, conjunctivitis, and injection-site reactions. Sustained improvement was seen up to 76 weeks in all efficacy outcomes, including measures of skin inflammation, pruritus, and quality of life (Deleuran et al., 2020). Apart from these studies by (Silverberg et al., 2020), (Alniemi & McGevna, 2019), (Cork et al., 2017), (Callewaert et al., 2020), (Schneeweiss et al., 2020), (Jo et al., 2020), (Strowd & Feldman, 2017), (Armario-Hita et al., 2019) and (Faiz et al., 2019) also reported positive outcomes, high efficacy and safety with respect of AD treatment in both adult and pediatric patients. However (Li et al., 2020) report a novel association between dupilumab use and potentially sight-threatening corneal ulceration. A comparative study suggested a higher relative efficacy of dupilumab compared with ciclosporin in the treatment of patients with moderate-to-severe AD (Ariens et al., 2018).

Human in vivo findings confirm IL-33 role in the therapeutic potential for IL-33 inhibition in human diseases, including AD. Studies on drugs such as Etokimab (Chen et al., 2019), GBR 830 (Guttman-yassky et al., 2018), KHK4083 (Nakagawa et al., 2020) and Lebrikizumab (Simpson et al., 2018) also reported positive and significant efficacy towards AD with known or mild adverse events. The infusion of Mesenchymal stem cells hucb-mscs was also discovered as an effective therapy for patients with moderate-to-severe AD, causing reduction up to 50 percent from baseline symptoms. (Kim et al., 2017). Treatment with R. Mucosa has been linked with significant decreases in estimated disease severity, topical steroid requirement, and S. Aureus burden (Myles et al., 2018).

Unconventional treatments such as Human breast milk HBM have been found equally effective if not more against traditional treatments such as hydrocortisone ointments for infants suffering from eczema with no potential adverse effects (Kasrae et al., 2015). Immunotherapies such as Prophylactic high-dose house dust mite (HDM) allergen oral immunotherapy is well tolerated in children at high heredity risk (Zolkipli et al., 2015). Other immunotherapies such as sublingual immunotherapy (SLIT) may be more expensive than conventional treatments, because it is an adjunctive therapy that improved not only the outcomes for atopic

dermatitis, but also its comorbid allergic conditions in canines (DeBoer et al., 2016), children (Chan et al., 2019) and adult human subjects (Liu et al., 2019).

Upadacitinib is another that has been frequently studied in last five years. It has been identified as a potential drug with mild adverse effects however its performance potential still needs further evaluation towards moderate to severe AD patients (De Bruin-Weller et al., 2018). In the pilot study by a dose-response relationship was observed for upadacitinib efficacy; the 30-mg once-daily dose showed the greatest clinical benefit. Dose-limiting toxicity was not observed (Guttman-Yassky et al., 2020). The most common treatment-emergent adverse events in the upadacitinib groups were upper respiratory tract infection (Khattri et al., 2017). Tralokinumab treatment has also been associated with early and sustained improvements in AD symptoms and an acceptable safety and tolerability profile however like Upadacitinib it is accompanied by upper respiratory tract infection (Wollenberg et al., 2019). Methotrexate was found inferior to Cyclosporine in AD patients. However, increasing the doses of Methotrexate induced a significant improvement versus cyclosporine at week 20. The adverse events were more frequent in association to cyclosporine despite its efficacy (Goujon et al., 2018).

Other treatments that showed successful potential in terms of efficacy and safety towards AD and Eczema symptoms included Oclacitinib (Marsella & Ahrens, 2018), Pseudoephedrine (Chen et al., 2020), Naringenin, a natural remedy (Nagula & Wairkar, 2020) and I. Inflexus (Thunb.) Kudo extract (IIE). It is a candidate anti-AD therapy due to its ability to exert neuro-protective and anti-depressant effects (Park et al., 2020). The most failed outcome was reported by clinical study on Secukinumab with minimal changes in the lesional profiles of the secukinumab treated groups at week 16 accompanied by severe adverse effects such as respiratory tract infections (Ungar et al., 2020). MOR106 also reported no significant improvement despite not reporting any adverse events either for AD patients (Thaci et al., 2018).

3.6. Risk of bias in literature review

The risk of bias assessment was performed to find out the potential systematic errors in our selected studies that may affect the outcome of this systematic review. A bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect. The risk of bias summary and graph were created using the Cochrane risk of bias tool (RevMan 5.4.1) in this study. The Cochrane Collaboration has developed a tool for assessing bias in clinical trials. The tool has been adopted across all Cochrane systematic reviews since 2008. Additionally, the tool is now widely used outside of Cochrane and has been utilized in our analysis.

Each of the fifty studies were critically screened by the researcher by following the Cochrane risk of bias assessment guidelines and criteria. The criteria assess each study on the basis of five types of risks which are Random sequence generation, Allocation concealment, Blinding of participants, Blinding of outcome assessment and incomplete outcome data as well as a sixth option of any other bias not identified by Cochrane standard.

Figure 3.4 and Figure 3.5 summaries 'Risk of bias' assessments. For overall risk of bias across studies, trials were at low risk of bias. We categorized eleven studies as being at high risk of bias reporting two or more high risk criteria. Among the high-risk group, studies six had less than two high 'Risk of bias' domain with all the other dimensions at low risk. We categorized the remaining one as being at unclear risk of bias because we assessed more than one criteria as unclear. The major high risk factor in studies was associated with the incomplete outcome data (attrition bias).

Allocation

The method of sequence generation was described in all randomized studies but case studies, open label studies and in vivo lab trials did not follow this protocol. Since maximum studies included in our review were controlled trials. So this criteria was considered as low risk of bias for these studies.

Blinding

Blinding of participants and personnel was achieved in all of our randomized trials studies excluding uncontrolled studies. The risk of detection bias was low for our included clinical studies.

Incomplete outcome data

Majority of the included studies did not lack any substantial outcome data, however seven studies were found at high risk of bias owing to missing outcome measures in their report. Major reason was found to be not mentioning reasons for discontinuation of particular sample group or missing data imputation.

Selective reporting

We considered 17 trials to be at high risk of selective outcome reporting because results for outcomes were mentioned but not in complete detail for each objective and measure specifically adverse effects of intervention and it affect the quality of reporting and create risk of confusion.

Other potential sources of bias

We opted out of filling the 'Other risk of bias' item as we did not search for assumed criteria as a scale to measure other risk of bias from specific trial setups, personal errors in experimental and control groups, and clinical settings.

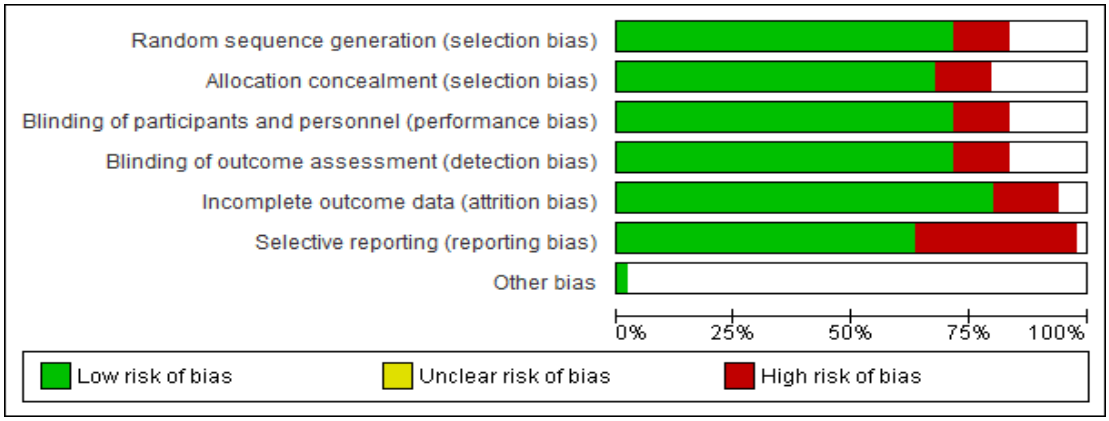

Figure 3.4 Risk of bias graphical representation for studies included in systematic review.

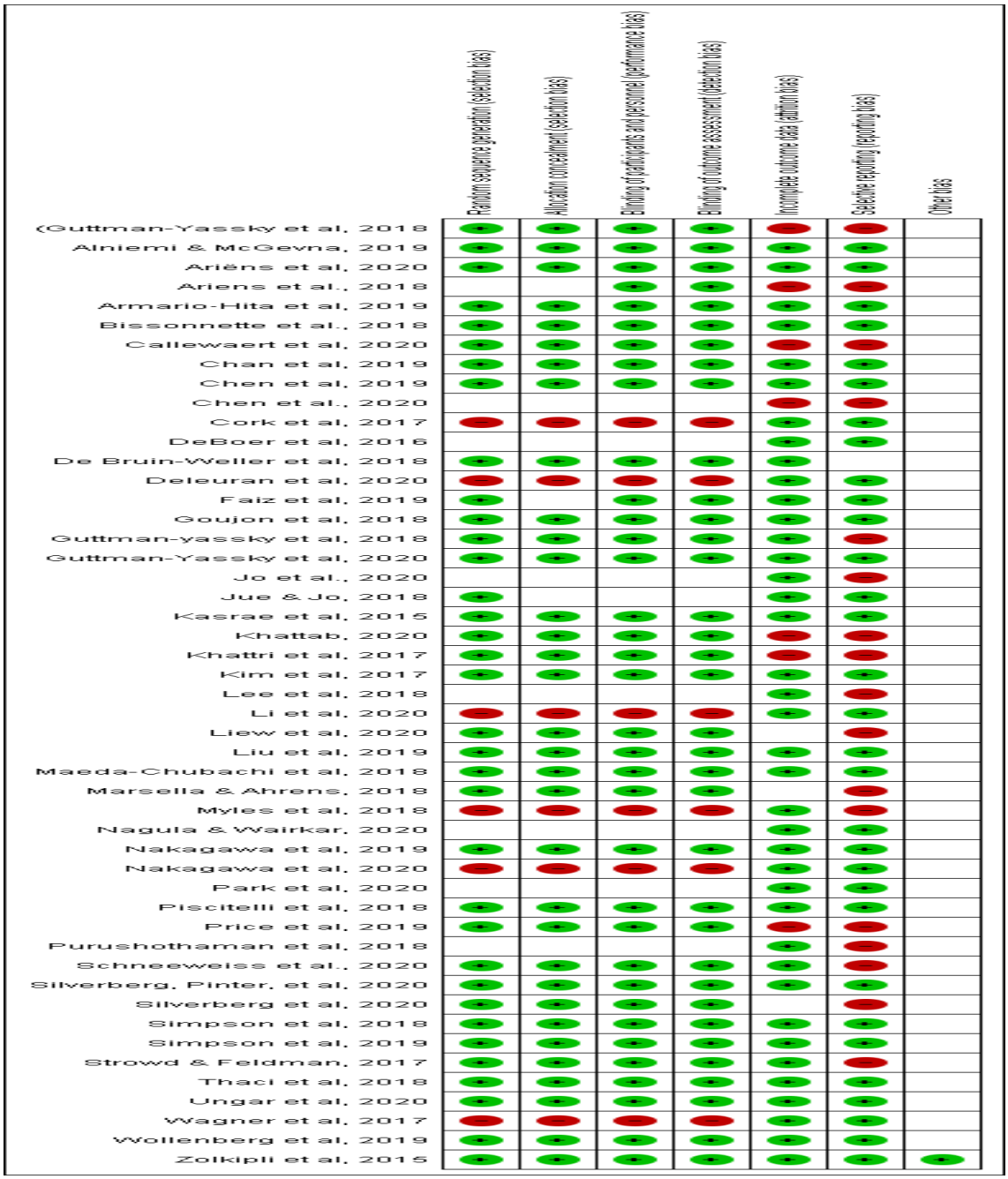

Figure 3.5. Risk of bias summaries for studies included in systematic review.

4.1. CONCLUSION

Atopic dermatitis is a persistent type of disease. Atopic dermatitis, also known as 'atopic eczema', is considered to be common and recurrent skin disease which causes chronic inflammation prevalent at any age group in both adults and children in both the less- developed and the industrialized countries of the world (Montes-Torres, Llamas-Velasco, Pérez-Plaza, Solano-López, & Sánchez-Pérez, 2015). The aim of this systematic review was to derive authentic biological therapies for the accurate treatment of AD in current advanced medical era. We addressed three objectives through this systematic review and collected the clinical trials involved with the biologics for AD treatment, then we determined the safety and efficacy of these therapies with respect to the placebo effect by utilizing qualitative analysis and discussion for heterogeneity assessment and finally we determined risk of bias in included studies that might influence our results. The literature search was completed and yielded a preliminary database of 2788 articles from the electronic databases, primarily PubMed and Cochrane Library (CINAHL, CT.gov, Embase, CTRP, PubMed). This initial pool of studies was reviewed, screened and filtered to determine eligibility. We minimized our pool of studies to fifty for this review presented as PRISMA flow diagram. This study provided a qualitative systematic review of different biologics used in the biological therapy and other clinical trials for the treatment of AD. In terms of achieving safety and efficacy with biological therapies therapy in trials, we found the following results, based on qualitative review. Primarily all of the assessed interventions (molecular and biological treatments) showed significant superiority compared with placebo. Most of the biological agents showed significant improvement for participants with positive safety and efficacy levels except for Secukinumab and MOR106. When compared with placebo and other agents, biological agent's dupilumab and ustekinumab are the best choices for attaining safe levels of treatment. In terms of risk of bias assessment and summaries our analysis concluded low risk of bias for most studies with few exception. However, more extensive studies are required with completely reported data to provide more proof about the efficacy and safety of biological therapies and to compare their safety profiles.

4.2. Implications for future research

In terms of theoretical aspects and implications, there are several broadened criteria that can be addressed when conducting future researches based on the findings from this systematic review. Future researches can focus on analyzing the methodological standards in these studies. Since a lot of the included and excluded studies presented extremely small sample sizes. The future studies can also analyze the scope of molecular therapies discussed in this systematic review individually in comparison to conventional treatments. It is imperative to ensure that when comparing the efficacy of a new treatment that it is compared to a gold standard which has a strong evidence base. This will ensure that the new approach is properly scrutinized and that conclusions drawn are valid. This systematic review will help further assess the potential of the treatment itself to ensure that the intervention is carried out as intended. Future researchers may uncover more biasness in data based on including secondary factors in addition to our moderator variables for the systematic review such as drug doses or demographics. Given that this systematic review, to the author's knowledge, is to primarily investigate the efficacy of modern or current biological therapies for Atopic dermatitis, all therapies were not discussed and future researchers can work on scrutinizing their potential as well.

On a practical implication note this systematic review can have major implications for potential clinical services and offer the prospect of delivering treatment to a large number of people. Our study holds extremely rich prospects for future studies and applications by providing evidence into impact. The following study was conducted with the objective to broaden the scope for future researches in context of an initial investigation like the one presented here contributes to a broader global understanding of the potential, thus providing insight into the needs for efficient treatment selection in terms of Atopic dermatitis treatment, however many studies were excluded as there it didn't contain our desirable information or variables. The low figure of studies can result in a reduction in qualitative weight of our outcomes. There is some heterogeneity in the design of the included trials. In particular, use of biological therapies differed between studies, which could affect the general assumption. Another limitation of our study is in terms of safety profile, we assumed that the response of studies irrespective of the doses and underlying diseases in participants as well as additional treatments being administered, we also didn't acknowledge the fact in our analysis that pharmaco-responsiveness for different kinds of treatments may duffer for atopic dermatitis patients. However, we cannot exclude the theoretical possibility 0f these circumstances. Given that this systematic review, to the author's knowledge, is to primarily investigate the efficacy of biological therapies for atopic dermatitis, all therapies were not discussed.

4.3. Summary of the chapter

This chapter provided detailed discussion of outcomes of our research design and analysis and their effect on the objectives of this systematic review and comparison to previous reviews or studies of same notion and design. The chapter also discussed the future implications of our study and contribution towards other research work in this direction. The limitation arising from our selected method for analysis and its impact on others were also discussed in the end.

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