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A Comparison of Measures to Determine Severity of Disease in Adults With Psoriasis: A Systematic Review

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A Major Paper Presented

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Abstract

Plaque psoriasis is an autoimmune disease of the immune system affecting many adults worldwide. Due to the inflammatory nature of the disease, adults with psoriasis are at higher risk for thromboembolic events including heart attack and stroke. Treatment options are offered based on the severity of disease and may have implications for reducing cardiovascular disease. Selecting a clinically validated tool to measure the performance of a treatment or therapy has implications for research and clinical practice and therefore it is important to understand the strengths, weaknesses, and limitations of measures used to describe the severity of illness in patients affected by psoriasis. Systematic reviews are research reviews that combine the evidence of multiple studies related to a specific clinical problem to inform clinical practice (Whittemore & Knafl, 2005). This systematic review of the literature examined the clinically validated tools used in large randomized controlled trials within the past ten years. The results of this study found that authors of major studies evaluating the effectiveness of treatment on adults with psoriasis used a combination of clinically validated tools to determine the severity of disease. The instruments chosen include the Psoriasis Area and Severity Index (PASI), the Static Physicians Global Assessment (sPGA), and Body Surface Area (BSA).

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A Comparison of Measures to Determine the Severity of Disease in Adults with Psoriasis: A Systematic Review

Background/Statement of the Problem

Psoriasis is a complex autoimmune disorder with a prevalence in Europe and North America at about 2%, according to the World Health Organization (WHO) (Boehncke, 2015). Mild forms of the disease account for nearly 70%-80% of all cases (Boehncke, 2015). Manifestations of the disease include plaque, accounting for 90% of all cases, arthritic, guttate, inverse, and pustular (Boehncke, 2015). The pathogenesis of psoriasis derives from dysregulation of the adaptive and innate immune system with dendritic cells producing pro-inflammatory cytokines in the exacerbation stage. These cytokines include Tissue Necrosis Factor-alpha (TNFa) and Interleukin 12, 23 and 17 (Boehncke, 2015). Successful use of inhibitors of these cytokines further supports the belief that psoriasis is an immune-mediated disease with genetic and environmental factors (Boehncke, 2015).

Psoriasis being an autoimmune inflammatory disease has the potential for developing into psoriatic arthritis (PsA) a subtype of psoriasis (Elmets et al., 2019). According to Elmets et al. (2019), PsA has an incidence rate of 30%-33% amongst adults with psoriasis. It is an inflammatory arthritis that affects both joints, tendons, and ligaments (Elmets et al., 2019). In fact, among patients with a 30-year history of psoriasis, the prevalence reaches about 20.5% indicating that the longer one lives with psoriasis, the greater the chance of developing PsA (Elmets et al., 2019). Therefore, screening for PsA is important in the management of adults with psoriasis. Psoriatic

arthritis may present as painful and swollen joints in the hands, feet, knees, and arm or spine and can be challenging to differentiate between other forms of arthritis (Elmets et al., 2019).

The importance of screening for PsA is to initiate prompt treatment and reduce further joint damage (Elmets et al., 2019). The C-Reactive protein, a test that measures inflammation is neither sensitive nor specific to confirm a diagnosis of PsA (Elmets et al., 2019). Tom et al. (2015) reiterates this point and state that it's crucial to have screening tools that can detect the presence of PsA as early as possible. The authors report that early treatment has the benefits of improving quality of life, reducing joint damage and greater longevity.

A paper published as a joint venture between the American Academy of Dermatologists (AAD) and the National Psoriasis Foundation (NPF) provides guidance in clinical decision making in the management of psoriatic disease (Elmets et al., 2019). Using an evidence-based model, the authors searched the literature to find critical clinical questions related to comorbidities associated with psoriasis (Elmets et al., 2019). The authors identified twelve comorbidities that are considered when either screening and or managing patients with psoriasis (Elmets et al., 2019).

The severity of psoriasis places patients at greater risk for comorbid conditions (Elmets et al., 2019). Chronic inflammatory diseases, such as psoriasis, are known risk factors for cardiovascular disease (Elmets et al., 2019). According to Elmets et al. (2019), the incidence of heart disease per 1000 person-years is 3.58 for the general population, increasing to 4.04 for patients with moderate psoriasis and 5.13 for patients with severe psoriasis. The authors also found that moderate and severe psoriasis are independent risk

factors for stroke (Elmets et al., 2019). One method for evaluating mortality in adults with psoriasis is the Major Adverse Cardiovascular Events (MACE), which is a composite endpoint used by researchers (Elmets et al., 2019). MACE comprises four events: heart failure, sudden cardiac death, myocardial infarction, and stroke falling under one umbrella (Elmets et al., 2019). The authors determined that psoriasis accounts for an additional 11,000 MACEs per year, underscoring the need for providers to discuss cardiovascular risk with their patients.

Metabolic syndrome is a cluster of chronic health conditions that play a significant role in mortality in patients with psoriasis (Elmets et al., 2019) The five conditions are increased abdominal girth, elevated triglycerides, low HDL cholesterol, an elevated blood pressure and high fasting blood sugar (Elmets et al., 2019). Metabolic syndrome is diagnosed when a person has three out of the five conditions (Elmets et al., 2019). In a comparison to practice-matched control patients, the authors reported that 34% of psoriatic patients meet the criteria for metabolic syndrome as compared to the control group in which 26% of the patients met criteria (Elmets et al., 2019). The authors also reported across the board, psoriasis patients scored higher for each individual component of metabolic syndrome as compared to control groups; obesity (385 versus 31%), elevated triglycerides (36% versus 28%), hypertension (31%versus 28%) and elevated glucose (22% versus 16%) (Elmets et al., 2019). The significance of these findings is that the prevalence of metabolic syndrome is higher in patients with psoriatic disease and worsens with disease severity (Elmets et al., 2019).

Treatment options for patients include conventional treatments and biologics (Boehncke, 2015). Conventional therapies include vitamin-D derivatives, phototherapy,

topical corticosteroids, homeopathic and oral immunosuppressive drugs like methotrexate, for example (Boehncke, 2015). Biologic agents are the newest available treatments that target the disease in a fundamentally different way. They are derived using monoclonal antibody technology and include Tissue Necrosis Factor Alpha (TNFa) inhibitors, interleukin 12 and 23 blockers (IL 12, 23), and interleukin 17A (IL-17A) blockers (Boehncke, 2015). Although slightly different, most guidelines do have a threshold for transitioning from conventional therapies to biologics (Golbari et al., 2018; Llamas-Velasco et al., 2017; Menter et al., 2019). Early screening and detection are essential to identify patients who may be candidates for biologic therapy (Elmets et al., 2019).

Practice guidelines for the treatment of psoriasis are evolving and will continue to change as new treatments become available (Golbari et al., 2018). According to Menter et al. (2019), the severity of psoriasis determines treatment. Menter et al. (2019) state that most patients with mild to moderate forms of the disease can be managed with topical medicine and phototherapy, whereas patients with moderate to severe forms of the disease should be managed with biologics alone or in combination with topical or systemic medicine. Currently there is no consensus amongst experts on how to classify the severity of psoriasis (Golbari et al., 2018). However, the professional organizations such as the National Psoriasis Foundation, the American Academy of Dermatology, the European Consensus Program, the European Dermatology Forum, the British Association of Dermatologists, and the Merit Based Incentive-Payment System (MIPS) publishing consensus statements use one or more validated tools such as the Psoriasis Area and

Severity Index (PASI), Body Surface Area (BSA) and subjective questionnaires, such as the Dermatology Life Quality Index (DLQI) (Golbari et al., 2018).

According to Golbari et al. (2018), systemic treatments must be considered for a BSA of 5%-10%, which is considered severe disease. They conceded this approach may be problematic because affected areas such as the palms, soles, hair, and genitals may be difficult to treat and should be classified as severe. They also reported that if the disease is causing psychological harm, then it should also be considered severe (Golbari et al., 2018). Menter et al. (2019) echoed this point but defined mild psoriasis as <3% BSA, moderate as 3% to 10% BSA and severe as greater than 10% BSA. Menter stated that the PASI is clinically important for appraising the patient's response to treatment but is not useful for guiding clinical practice or management of the disease (Menter et al., 2019). In contrast, Llamas-Velasco et al. (2017) reported that the PASI is the most used scale to measure the severity of psoriasis and drive clinical decision making. Regardless of how the disease is measured, the authors agree that patients fall into either mild or moderate to severe classification. The authors also agree that mild disease can be managed with conventional therapy and moderate to severe forms should be managed with biologics.

In addition to recommendations set forth by professional organizations, it is also necessary to consider what payers are willing to cover. Menter et al. (2019) stated that moderate to severe forms should be treated with biologics but Golbari et al. (2018), made a valid point that many insurance companies may require a trial of oral systemic drug treatments and phototherapy before considering biologics. In contrast, Chi and Wang (2014) stated the societal costs associated with not prescribing biologics, including increased hospitalization costs, and lost productivity to name a few, offset any savings

with less effective medicines. Biologic drugs are amongst the highest priced medications used to treat psoriasis (Chi & Wang, 2014). The price in 2010 for the most prescribed biologics, in US dollars ranges from a low of $13,429 for infliximab to a high of $33,574 for 90mg of ustekinumab for a 6-month supply (Chi & Wang, 2014). To evaluate the high costs associated with biologic therapy, Chi and Wang (2014) performed a cost-effective analysis by calculating the incremental cost-effectiveness ratio (ICER) to achieve a PASI 75, a reduction in symptoms by 75%, and sPGA 0/1. The authors found adalimumab likely to be the most cost-effective at $21,315 per PASI 75 responder, and ustekinumab 90mg the most expensive at $1,358,900. Chi and Wang (2014) concluded from their work that cost must be considered by clinicians and policy makers when allocating resources.

Psoriasis is a complex, autoimmune disease that manifests as disease of the skin and joints (Boehncke, 2015). There are many tools for evaluating the severity of disease but there is no consensus for which tool is the best choice. Regardless of which clinical guidelines are used, providers have the flexibility to prescribe what they feel is in the patient's best interest.

Therefore, the clinical question explored in this systematic review is, in adults with psoriasis, is there a measure (or measures) of severity of the disease to guide appropriate treatment options?

Literature Review

Several sources were used in this literature review including: CINAHL, Academic Search Premiere at EBSCO*host*, Medline at OVID and PubMed@Tufts. Key terms searched were psoriasis, severity of illness, and randomized controlled trial. This literature review will examine the current literature describing clinically validated instruments used to determine the severity of illness in adults with psoriasis.

Screening Tools for Psoriatic Arthritis

Mishra et al. (2017) compared four validated screening tools used to diagnose psoriatic arthritis. The authors performed a noninterventional, cross-sectional analysis to determine sensitivity and specificity of the Toronto Psoriatic Arthritis Screen 2 (ToPAS 2), the Psoriatic Arthritis Screening and Evaluation (PASE), the Psoriasis Epidemiology Screening Tool (PEST) and the Early Arthritis for Psoriatic Patients (EARP) questionnaires. The authors found the highest sensitivity with EARP and the highest specificity with the ToPAS 2. These tools measure and have established specificity and sensitivity for evaluating the presence or absence of PsA.

Use of Multiple Screening Tools

Internal consistency and reliability of instruments used to score the severity of psoriasis has made the task of evaluating efficacy of treatments challenging. A systematic review by Spuls et al. (2010), found that amongst the 44 available scoring tools for determining the severity of plaque psoriasis none were clinically validated. The authors suggested that the best tool may be a combination of tools or ones that specifically measure a desired attribute. To validate three of the most used instruments, Bozek and Reich (2017) performed a cross-sectional study to determine both intra-rater

and inter-rater reliability of three tools used to measure the severity of psoriasis: the Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), and Static Physicians' Global Assessment (sPGA). The authors observed ten practicing dermatologists who evaluated the severity of psoriasis in nine individuals affected with plaque psoriasis over the course of a day. Bozek and Reich (2017) used statistical analysis to determine the inter-rater and intra-rater reliability. The authors found that the sPGA had the highest inter-rater reliability and the BSA had the highest intra-rater reliability. The authors found intermediate values for the PASI and concluded that there is no one tool that is superior. Bozek and Reich (2017) suggested that the best assessment requires several scoring tools used together, simultaneously. The authors acknowledged the low sample size of 9 participants may be a limitation but claim that each observer made over 50 assessments on each participant.

One Possible Solution Using the Low PASI Scoring Tool

Many researchers question the utility of the PASI tool in cases where the involvement of disease is limited to small areas (Otero et al., 2015). To address these concerns, Otero et al. (2015) performed a cross-sectional study to compare a new tool, the low PASI to the original PASI and to evaluate the inter-observer reliability between the two tools. The authors enrolled the patients who were older than 18 years, with mild to moderate psoriasis and a total affected area of less than 10%. The authors then had two experienced assessors evaluate each participant independently. Otero et al. (2015) used linear mixed models to determine the inter-observer correlations between the low PASI and PASI score. The authors found excellent inter-observer agreement amongst both observers for each instrument. In conclusion, the authors contended that the low PASI

scoring tool may provide more precise scoring for patients affected by psoriasis in less than 10% of their body area. The authors stated that the utility of the classic PASI score diminishes in areas of minimal involvement. The authors claimed the low PASI is not a substitute for the PASI but aids in providing a better assessment when affected areas are small.

Statistical Solution Using the Intra-Class Correlation Coefficient

Two systematic reviews (Puzenat et al., 2010; Spuls et al., 2010) that examined the validity of severity and outcome instruments designed to measure the degree of psoriasis failed to find one such tool. Researchers are still questioning the validity of the most used instruments to determine the severity of psoriasis. One potential pitfall lies in the way inter-rater agreement is derived through statistical analysis. To provide a more realistic analysis, Gourraud et al. (2012) performed a simulation study by two practitioners, based on an ongoing multicenter French study with 105 participants affected by moderate to severe psoriasis who were eligible for systemic or biologic therapy. The authors simulated a mixture of exponentially decreasing and normal distributions of PASI scores to obtain 100 PASI scores sampled randomly out of 1000. Gourraud et al. (2012) took this approach because they felt the normal distribution of PASI scores is inherently skewed to the right and to overcome this limitation needs to be analyzed as a normal distribution. The authors found that the intra-class correlation coefficient (ICC) is preferable to other statistical methods for assessing inter-rater agreement when normal distributions do not exist, such as in the case of PASI.

PASI in clinical Practice

For randomized controlled trials (RCT), some experts suggest that PASI 90 (a 90% improvement in symptoms) should be used as an endpoint instead of the current PASI 75 (a 75% improvement in symptoms) (Norlin et al., 2020). In the clinical setting, a PASI 90 may not be a realistic goal because many individuals affected with psoriasis are transitioning from one treatment to another. To further explore this cause for concern, Norlin et al. (2020) performed a regression analysis to determine which factors are linked to achieving higher PASI scores in a clinical setting. A secondary aim was to look at health related quality of life (HRQoL) measures such as the dermatology life quality index (DLQI) and to find associations between improved quality of life and higher scores. The authors found that the absolute PASI score before switching to a biologic was associated with a higher PASI percentage after the switch. The authors reported that in clinical practice, there is no washout period as there is in randomized control studies and therefore no baseline for comparison as treatments are modified, added to, or switched. For this reason, Norlin et al. (2020) argued that PASI 90 is not a realistic goal in clinical practice.

Lack of Consensus Amongst Experts

There are many tools for evaluating the severity and outcomes for adults newly diagnosed with psoriasis, but there is no consensus about which instrument is the best choice (Golbari et al., 2018; Llamas-Velasco et al., 2017; Menter et al., 2019). The Psoriasis Area and Severity Index (PASI) is considered the gold standard and is used widely amongst researchers as a primary endpoint alone or in conjunction with other tools to measure the effectiveness of medications. Examples of studies using PASI

include a study by Busard et al., (2017) entitled, “Optimizing adalimumab treatment in psoriasis with concomitant methotrexate (OPTIMAP)”, and a study by Thaci et al., (2015) entitled, “Secukinumab is Superior to Ustekinumab in Clearing Skin of Subjects with Moderate to Severe Plaque Psoriasis: (CLEAR)”.

Summary

Gaps exist in the literature for describing clinically validated instruments used for evaluating the severity of psoriasis. This systematic review addressed the gap by examining and synthesizing the findings of randomized controlled trials that are used to measure the severity of disease in adults with psoriasis.

Theoretical Framework

Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms (TOUS) developed by Lenz et al. (1995) grew naturally from students working together describing the phenomena of unpleasant symptoms. The underpinnings of TOUS constructs describe the concepts of physiologic, psychologic, and situational factors that affect symptoms in duration, intensity, quality, and distress. Patients' symptoms affect performance in the areas of functional status, cognitive functioning, or physical performance. In essence, patients' symptoms often occur in combination with other signs and or stressors; for example, pain and fatigue may be made worse by financial or family issues (Lenz et al., 1995).

This middle-range theory frames the clinical context of psoriatic disease by understanding the relationship between unpleasant symptoms and quality of life. Individuals affected by psoriasis may experience disfigurement, chronic pain, itching and alterations in body image (Boehncke, 2015). It is important for providers to appreciate the extent to which the disease plays a role in interfering with quality of life and self-esteem. Having a model such as TOUS assists in understanding the relationship between the effects of disease severity and quality of life.

Method

Purpose

This systematic review of the literature compares and synthesizes research that examines measures used to determine the severity of disease in adults with psoriasis. Systematic reviews and Meta-Analyses offer the highest level of evidence to inform clinical practice and support evidence-based practice. Selecting a clinically validated tool to measure the performance of a treatment or therapy has implications for research and clinical practice and therefore it is important to understand the strengths, weaknesses and limitations of measures used to describe the severity of illness in patients affected by psoriasis.

Inclusion/Exclusion Criteria

This systematic review compared and synthesized data from randomized controlled studies to evaluate tools used to determine the severity of disease in adults with plaque psoriasis found in peer review journals published from 2010 until 2022 unless groundbreaking or foundational.

Exclusion criteria include non-English papers, non-randomized control trials, and articles published earlier than 2010.

Search Strategy

The following databases were searched for published articles: CINAHL, Academic Search Premiere at EBSCO*host*, Medline at OVID and PubMed@Tufts. References from retrieved articles using an ancestry approach were used to search the literature. Key search terms include psoriasis, randomized controlled trials, and severity of illness. Results were further refined by limiting studies to the past 10 years, for all

adults, and published in scholarly, peer reviewed journals. Duplicate and unretrievable articles were excluded. Phase one retrieval excluded all studies that were not randomized controlled trials. In Phase two, studies were excluded if they were not a primary source, or if the primary endpoint of the study was measuring something other than response to treatment, such as a drug concentration measurement, tolerability of a drug, safety of a drug, or immunogenicity of a drug. Studies were also excluded if they were not blinded, if the study only examined mild forms of plaque psoriasis and excluded moderate or severe forms of plaque psoriasis, or if the measures were to evaluate relationships between two or more variants of psoriasis. Although there are many types of psoriasis, the focus of this systematic review is plaque psoriasis, accounting for over 90% of psoriasis cases (Boehncke, 2015). Search results were systematically recorded using Endnote 20 for clarity and reproducibility.

Data Collection and Synthesis

Data were extracted and entered manually into an evidence summary table (Appendix A) created in excel to appraise, analyze, and compare studies. Essential information extracted included - study title, authors, purpose, theory, type, design, variables, population, sampling, data collection, measurements, reliability, analysis, significance, limitations, transferability, level of evidence, and relevance to nursing.

Critical Appraisal Tools

The Critical Appraisal Skills Programme (CASP) (Appendix C) (Critical Appraisal Skills Programme UK, n.d.) was used to evaluate the quality of evidence supporting the use of diagnostic instruments designed to rate the severity of psoriasis. The CASP appraisal tool is an accepted method for assessing the strengths and

weaknesses of literature affecting healthcare policy or practice (Singh, 2013). A list of discarded studies and description of why they were not selected was maintained.

Outcome Criteria

The outcome criteria were the measurable changes reported by the authors in the RCTs selected for this systematic review.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as a method for study search, selection, screening and applying inclusion and exclusion criteria. This flow diagram provided a high-level view of records reviewed, screened, and included or excluded from the study.

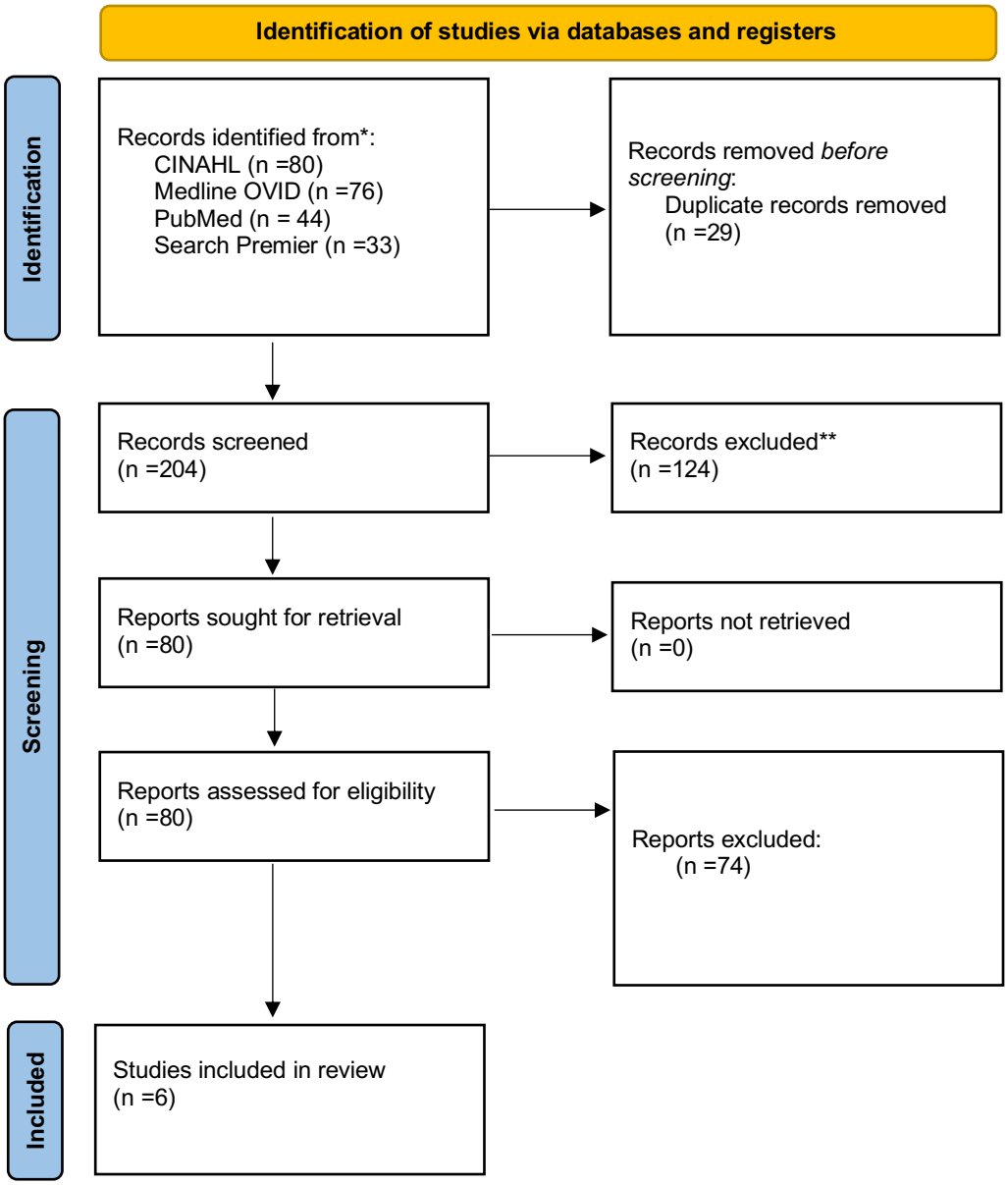
Cross Analysis

Data were entered into a cross-study analysis table (Appendix D) and studies were compared for diversity or similarities.

Results

Figure 1

Identification of studies via databases and registers



Note: Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., … Moher, D. (2021).

The PRISMA diagram in Figure 1 represents data extracted from the following databases: CINAHL, Medline OVID, PubMed, and Search Premier. Search criteria included adults with psoriasis, severity of symptoms and randomized controlled trial from 2011 to 2021. The initial search yielded 233 results after removing for duplicates and articles not available, 204 articles were included in phase one retrieval. Systematic reviews and meta-analyses were excluded in phase two eligibility, which equaled 124 articles removed, leaving 80 for phase two eligibility. In phase two, 74 articles were excluded if they were non-randomized, or if they were not a primary source, or if the primary endpoint of the study was measuring something other than response to treatment, such as a drug concentration measurement, tolerability of a drug, safety of a drug, or immunogenicity of a drug. They were also excluded if the study was not blinded, or if the study only examined mild forms of disease and excluded moderate or severe forms of psoriasis or if the measures evaluated relationships between two or more variants of psoriasis. The final number selected n=6 were double blinded randomized controlled trials of sufficient power to measure the degree of an intervention, targeting psoriasis vulgaris with a primary endpoint of reduction in disease severity using a method described by the authors of each study.

The studies selected were double blinded, randomized controlled trials of adults with plaque psoriasis with sample sizes large enough for normal distribution with enough power to show a clinically significant improvement in symptoms. Study specific data are found in Tables A1 through A 8 with descriptions for the purpose of the study, the design, where the study took place, the sample size, methods, and procedures for collecting data. Outcome data are found in Tables B1 through B8 and describe variables

of interest, the treatment arms comparing either treatment versus placebo, treatment A versus treatment B, or different strengths of a treatment versus placebo. Outcome criteria also included risk difference and confidence or significance level. Tables C1 through C8 apply the critical appraisal tool to systematically appraise the evidence. The cross-study analysis summarizes the data in a format that allows for analysis and synthesis of the data.

Individual Studies

Leonardi et al., (2020) (Appendix A - 1) conducted a double-blinded randomized controlled trial designed to investigate whether risankizumab is an effective and safe medication for reducing the severity of symptoms in adults with psoriasis. The major points of the study were that patients treated with risankizumab versus placebo achieved significant improvement in their symptoms at 16 weeks and with continued use as compared to withdrawal of treatment at weeks 52 and 104. A major criticism of this study is that it did not assess the correlation between loss of efficacy and impact on quality of life. The design was a double-blind, randomized, placebo-controlled, two-part study taking place in 60 sites including: Australia, Belgium, Canada, the Czech Republic, France, Germany, Japan, South Korea, and the United States of America. The investigators enrolled adults, older than 18 years of age with moderate to severe chronic plaque psoriasis, for at least 6 months. The authors selected patients with a body surface area of 10% or more, a Psoriasis Area and Severity Index of 12 or more and a Static Physicians Global Assessment score of 3 or more. Patients were excluded if they were not candidates for systemic or UV phototherapy. Baseline characteristics were predominantly male of the white race, weighing less than 100 kg, mostly with moderate psoriasis and a little over fifty percent having received previous biologic therapy. This was a two-part study. The intervention in part A randomized patients in a 4:1 pattern to receive risankizumab 150 mg or placebo for weeks zero to sixteen. At the end of part A (16-28 weeks), patients unresponsive to placebo were crossed over to start risankizumab 150 mg and continued for 28-88 weeks. Patients in the initial part A treatment group, of risankizumab 150 mg were randomized based on their sPGA score starting at week 28.

Patients with an sPGA of 0/1 were randomized to risankizumab 150 mg or to placebo (withdrawal of treatment). For those randomized to 150 mg at week 28, if they had an sPGA of 3 or more by week 32, they were assigned to open label risankizumab 150 mg. In the placebo (withdrawal group), if after 32 weeks had an sPGA of 3 or more were assigned to open label risankizumab 150mg. The co-primary outcomes of PASI 90 and sPGA 0/1as detailed in table B-1, shows a significant ($p<0.001$) improvement in PASI and sPGA scores in patients assigned to risankizumab as compared to placebo in parts A and B. Secondary outcomes measuring adverse events found no attributable events directly related to risankizumab.

Lebwohl et al., (2020) (Appendix A – 2), conducted a parallel-group, double-blind, placebo control study among adults with mild, moderate, or severe psoriasis at risk for worsening symptoms. The researchers investigated whether roflumilast cream, a phosphodiesterase type 4 inhibitor (PDE-4) reduces the severity of disease as compared to placebo. The major point of this study were that a cream form of an oral PDE-4 medication is efficacious in reducing the severity of symptoms in plaque psoriasis. Criticisms of this study are the short duration - 12-weeks of treatment and evaluating primary endpoints at week 6. Additionally, a small subset of patients with intertriginous (15%) psoriasis was too small to be statistically significant. The design was a parallel group, double blind, randomized, placebo-controlled study. The population selected was adults 18 years or older with at least mild psoriasis indicated by an investigators' global assessment (IGA) score of 2 or more on a 5-point scale, a BSA of at least 2% but not more than 20%, and a modified PASI score of 2 or more (72-point scale). Patients were excluded if they received above average exposure to UV radiation,

variants of psoriasis including pustular or guttate or the inability to discontinue cytochrome p450 inducers or inhibitors. Also excluded were patients currently taking oral PDE-4 inhibitors. Baseline characteristics were about half women and half men, mostly of the white race, and most with moderate psoriasis on the IGA scale. The interventions were randomized to 1:1:1, either roflumilast cream 0.3%, roflumilast cream 0.15% or vehicle cream (placebo) and were applied once daily to affected areas for 12 weeks. The primary outcome was an IGA score of 0 or 1 at week 6, a secondary assessment was made for intertriginous only at baseline. Secondary outcomes were BSA and PASI scores and patient reported Worst Itch Numeric Rating Scale (WI_NRS). Also included in the secondary outcomes were the Psoriasis Symptom Diary score and the Dermatology Life Quality Index. Adverse effects were monitored with investigator site assessments, laboratory studies, 12-lead EKG, vital signs, a health, and suicide questionnaire. As seen in Table B-2 both roflumilast cream 0.3% and 0.15% showed a clinical reduction in symptoms at week 6 measured by an IGA score of 0 or 1 as compared to vehicle cream with a significance level of P=0.001and P=0.004 respectively, however comparisons could not be made between roflumilast cream 0.3% and roflumilast cream 0.15%. There was no plan for multiple comparisons of the secondary outcomes and therefore no conclusions were made, although the authors note the PASI scores were in the same general direction as the primary outcome.

Papp et al., (2017) (Appendix A – 3) conducted a randomized, double-blind randomized controlled study to answer the question, among adults with moderate to severe plaque psoriasis, are the biosimilar drug ABP 501 and adalimumab equivalent at reducing the severity of symptoms in psoriasis. The major findings of this study show no

difference between ABP 501 and adalimumab in terms of efficacy or safety. A major criticism of this study is the lead author disclosed an association with Amgen, the maker of ABP 501 who provided funding, and participated in many aspects of the study, including design, analysis, and approval of the manuscript. The population selected for this study was adults 18 to 75 years old with stable moderate to severe psoriasis for at least 6 months, who were eligible for UV photo or at least one conventional systemic therapy. Patients were required to have a BSA of at least 10% and a PASI score of at least 12 and a sPGA score of at least moderate on a 6-point scale. Exclusion criteria included active tuberculosis, women of childbearing age unable to take contraception, patients with types other than plaque psoriasis or have skin conditions that may interfere with assessing the severity of disease. Additional criteria included no systemic therapies within 28 days of enrollment and topical therapy limited to upper mid strength and emollients. Baseline characteristics were mostly men in their 40s, predominantly of the white race, with mostly moderate psoriasis on the sPGA scale. Patients were initially randomized 1:1 to receive ABP 501 80 mg on week 1, followed by 40mg week 2 and every 2 weeks thereafter, or adalimumab 80 mg on week 1, followed by 40 mg week 2 and every 2 weeks thereafter up to week 16. After week 16, patients in the ABP 501 group with a PASI 50 or better continued for an additional 32 weeks. Patients in the adalimumab group with a PASI 50 or better were re-randomized in a 1:1 to ABP 501 or adalimumab for an additional 32 weeks. As seen in Table B-3 the primary endpoint was precent improvement in PASI from baseline, ABP 501 showed an 80.9% improvement and adalimumab showing an 83.1% increase from baseline, statistically demonstrating

clinical similarity. Additionally, measurements for PASI 75, 90, 100 and sPGA 0/1 demonstrated clinical similarity. Safety and adverse events were not clinically different.

Papp et al., (2018a) (Appendix B – 4) conducted a double-blind, randomized controlled study among adults with psoriasis to see if tyrosine kinase 2 inhibition (TYK2) drugs, such as BMS-986165 is effective at reducing the severity of symptoms in psoriasis. The major points of this study are that elective inhibition of TYK2 is superior to placebo in reducing the severity of symptoms. A major criticism of this study is that it was sponsored by the drug maker, Bristol-Myers Squibb, who supplied the product and had oversight over the design, monitoring, and analysis of the results. The trial design was a double-blinded, placebo controlled, multinational study taking place in 82 sites in the United States, Japan, Poland, Canada, Germany, Latvia, Mexico, and Australia. The population selected were adults with plaque psoriasis for more than 6 months, eligible for UV or systemic therapy, a BMI between 18 and 40 who had moderate to severe psoriasis defined by an affected body area of more than 10%, a PASI score of 12 or more and an sPGA score of 3 or more. Exclusion criteria were non-plaque psoriasis, other immune disorders requiring immunosuppressive therapy, certain types of infections, such as hepatitis B or C, tuberculosis, or previous lack of response to any agent targeting interleukin 17 or 23. Baseline characteristics of the patients were predominantly male, in the mid 40s, mostly of the white race with a BMI in the 20s. Patients were randomly assigned in a 1:1:1:1:1:1 pattern of the drug BMS-986165 to either 3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily or 12 mg daily or identical looking placebo for 12 weeks. Patients assigned to twice daily took the drug every 12 hours. The drug was blinded to patients and investigators by using combinations of 3 mg capsules

with placebo. The primary endpoint as seen in Table B-4 was the PASI 75 score, with significant improvement in PASI 75 for the 3 mg daily (39% improved), 3 mg twice daily (69% improved), 6 mg twice daily (67% improved) and 12 mg daily (75% improved). Likewise, improvements were seen in secondary outcomes for PASI 50, 90 and 100 as well as sPGA 0/1 and DLQI as seen in Table B-4. The authors reported more frequent adverse events in the intervention arms as compared to placebo and reported one case of melanoma in the 3 mg daily group.

Papp et al., (2018b) (Appendix B-5) conducted a randomized, double-blind, placebo-controlled study among adults 18 years or older to determine if bimekizumab (BZK) an interleukin 17a and 17f inhibitor was effective at reducing the severity of symptoms in adults with psoriasis as compared to placebo. The major points of this study were if interleukins 17a and 17f play a role in worsening inflammation associated with psoriasis. Drugs, such as bimekizumab, neutralize both interleukin 17a and 17f targeting specific steps in the inflammatory process. A major criticism of the study is the lead author was a consultant for the biopharmaceutical company Union Chimique Belge (UCB) who funded this research. The design was a multinational randomized, double-blinded, placebo controlled, parallel group taking place in Canada, the Czech Republic, Hungary, Japan, Poland, and the United States. The population consisted of adults, 18 years or older, with a diagnosis of moderate to severe plaque psoriasis, for more than 6 months defined by a PASI of 12 or more, affecting more than 10% of BSA and a sPGA of 3 or more on a 5-point scale. Patients also needed to be eligible for UV or oral systemic therapy. Exclusion criteria included patients who have previously taken anti-interleukin 17 therapy or who have used a biologic in the past year for psoriatic arthritis.

Also excluded were patients with a history of a suicide attempt or suicidal thoughts within the past 6 months or a neuropsychiatric disorder. Baseline characteristics were mostly men, of white ethnicity, in their mid 40s, most with a history of other types of treatments including photo, anti-TNF, other biologics and systemics. Patients were randomized in a 1:1:1:1:1:1 pattern to receive bimekizumab every 4 weeks at doses of 64 mg, 160 mg (with 320 mg loading), 320 mg, 480 mg, or placebo. Both drug and placebo were administered at investigational sites by unblinded study personnel since the drug comes packaged as 160 mg/ml. As seen in Table B-5, as compared to placebo, all dosing for BZK achieved the primary endpoint PASI 75 improvement at 61.5%, 81.4%, 85%, 93% and 83.7% respectively at week 12. Similarly, secondary endpoint achievements in PASI 90, 100 and IGA 0/1 at 12 weeks were made as detailed in Table B-5. The significance level for all statistical testing was set to $p<0.001$. Safety considerations noted by the researchers included two patients reporting serious adverse events, one in the placebo group developed viral meningitis and one in the treatment group developed a large intestinal polyp and colon cancer. Other adverse effects in the treatment groups were fungal infections (4.3% affected).

Warren et al., (2021) (Appendix A – 6) conducted a randomized, double-blind, placebo-controlled study among adults with plaque psoriasis to evaluate the effectiveness and safety of bimekizumab against adalimumab in plaque psoriasis. The major points of this study were bimekizumab showed noninferiority and superiority as compared to adalimumab in achieving PASI 90 and IGA 0/1 response but did have adverse events, notably oral candidiasis, and diarrhea. A major criticism of this paper is that funding was provided by UCB, the biopharmaceutical maker of bimekizumab. UCB also provided

statistical analysis and required confidentiality agreements for the researchers. The design was a double-blind comparison of bimekizumab and adalimumab at 77 sites across 9 countries for a 56-week period. The population was adults 18 years or older, with moderate to severe plaque psoriasis lasting for more than 6 months. Moderate to severe disease was defined as PASI of 12 or more, a BSA of 10% or more, and an IGA of 3 or more on a 5-point scale. Exclusion criteria were previous exposure to either test drug and non-responders to anti-interleukin 17 agents or any biologic agent. Baseline characteristics were predominantly white males in their mid 40s, weighing about 90 kg, with about 25% BSA, two thirds with moderate psoriasis and one third with severe psoriasis. Patients were randomized 1:1:1 and assigned to either bimekizumab 320 mg every 4 weeks to week 16, followed by bimekizumab 320 mg, every 4 weeks to week 24 and week 56, or bimekizumab 320 mg every 4 weeks to week 16 followed by bimekizumab 320 mg every 8 weeks to weeks 24 and 56, or adalimumab 40 mg every 2 weeks, continued through weeks 16 and 24, then switched to bimekizumab 320 mg every 4 weeks until week 56. The drugs were administered subcutaneously in clinic and were blinded to all except those staff who prepared and administered the drugs. The primary endpoints as seen in table B-6, shows noninferiority and superiority of bimekizumab (86.2%) over adalimumab (47.2) achieving PASI 90 and IGA score of 0/1 (85.3% and 57.2% respectively) at week 16. Secondary endpoints as seen in Table B-6 trend in the same direction for PASI 100 at weeks 16 and 24 and PASI 75 at weeks 16 and 24. IGA scores of 0/1 at week 24 showed the same noninferiority and superiority. There were more adverse events including one death in the bimekizumab group, a 50-year-old man with squamous cell carcinoma of the tongue, 6 weeks after starting bimekizumab and

dying 5 months afterward. The authors reported oral candidiasis and diarrhea occured more commonly in the bimekizumab group as compared to the adalimumab group. Serious adverse events occurred in 5 patients receiving bimekizumab and 5 patients receiving adalimumab.

Cross-Study Analysis

The cross-study analysis (Appendix D) describes the drug-drug or drug-placebo comparisons made in each study, the primary and secondary endpoints, the validated instruments used for evaluating the severity of psoriasis and the results of each study. Blauvelt et al., (2020) compared risankizumab to placebo with primary outcomes of PASI 90 and sPGA 0/1, secondary outcomes were PASI 75, PAI 100, sPGA 0 and DLQI 0/1 and adverse events. Lebwohl et al., (2020) compared preparations of a PDE-4 cream compared to vehicle cream with the primary outcome being IGA 0/1 and secondary outcomes being IGA 0/1 plus 2-grade improvement, IGA scores at target weeks, PASI 50, 75 and 90, and WI-NRS scores.

Papp et al., (2017) compared a biosimilar drug, ABP 501against adalimumab for efficacy and safety. The primary efficacy end point was the percent improvement in PASI from baseline to week 16. PASI 50 and PASI 75 responses, sPGA /01. Secondary end points were safety and monitoring for treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), laboratory data, vital sings, and immunogenicity. Papp et al., (2018a) compared various dosing of a TYK-2 drug against placebo. The primary end point was a 75% or better reduction in the baseline PASI score at week 12. Secondary end points were PASI 50, PASI 90, PASI 100 sPGA 0/1 and DLQI at 12 weeks. Papp et al., (2018b) compared various dosing of bimekizumab to placebo. Primary efficacy end

point was the PASI 90 at week 12. Secondary end points were PASI 90 at week 8, PASI 75 and PASI100 at week 12 and IGA with equal or >2 categories of improvement from baseline at weeks 8 and 12. Warren et al., (2021) compared bimekizumab to adalimumab in a noninferiority study. The primary end points were PASI 90 at week 16 and IGA 0/1 with a 2-grade improvement from baseline at week 16. Secondary end points were PASI 100 at week 16, PASI 75 at week 4, PASI 100 at week 24 and IGA 0/1 at week 24. Exploratory end points were DLQI score 0/1at week 25 with PASI 90 and PASI 100 and DLQI score 0/1 at week 56 for patients switched from adalimumab to bimekizumab and did not have a PASI 90 or DLQI 0/1 score at week 24.

All studies used a validated instrument or instruments for evaluating the severity of psoriasis but differed in their methods. Study 1 used the PASI ≥ 12 (0 to 72) scale, sPGA ≥ 3 (0 to 4) scale and BSA ≥ 10%. The authors noted that a PASI 75 (or 75% improvement in symptoms) is consider clinically significant. They describe the PASI ranging from 0 (no disease) to 72 (maximal disease) and sPGA ranging from 0 (clear) to 4 (severe). Study 2 used the IGA ≥ 2 (0 to 5) scale, Modified PASI ≥ 2 (0 to 72) scale, WI-NRS (0 to 10) scale and Psoriasis Symptom Diary score (16 item scale) each item (0 to 10) scale The authors noted the IGA score ranges from 0 (clear), 1 (almost clear) to 4 (severe) and the modified PASI ranging from 0 (no disease) to 72 (maximal disease) The authors described the modified PASI as a tool they developed for measuring, with precision, areas of limited disease. Anatomical areas 1 to 9% were recorded as a fraction rather than a whole number, allowing for derivation from all elements of the PASI score. Study 3 used the PASI ≥ 12 (0 to 72) scale, sPGA “moderate” (0 to 6) scale and BSA ≥10%. The authors described the PASI as higher scores indicating more severe disease

and sPGA as ranging from clear to very severe. Study 4 PASI ≥ 12 (0 to 72) scales, sPGA moderate (0 to 5) scale and BSA ≥ 10%. The authors reported that the patient's handprint represents 1% of body surface area. They described the PASI as a summed score of redness, thickness, and scaliness of psoriatic skin lesions, involving the arms, legs, trunk, and head, ranging from 0 to 72 with higher scores indication severe disease. They described the sPGA ranges from 0 (clear) to 5 (very severe disease). Study 5 used the PASI ≥ 12 (0 to 72) scale, sPGA "moderate" (0 to 5) scale and BSA ≥ 10%. The authors did not describe the clinically validated instruments however, they did define abbreviations used: for example, the PASI 75: is a ≥75% reduction in baseline Psoriasis Area and Severity Index. Study 6 used the PASI ≥ 12 (0 to 72) scale, IGA ≥ 3 (0 to 5) scale and BSA≥10%. The authors stated the PASI score ranges from 0 to 72 with higher numbers indicating severe disease. They stated the IGA ranges from 0 (clear) to 4 (severe disease).

Blauvelt et al., (2020) concluded in their study Part A (73.2%) treatment arm versus (2.0%) placebo achieved PASI 90 Part B treatment arm intention to treat analysis (74% & 83.8%) achieved PASAI 90 and sPGA 0/1 at week 16 versus placebo at (2% & 6.1%). Lebwohl et al., (2020) concluded in their study 28% of the roflumilast 0.3% group showed an improvement, 23% of the roflumilast 0.15% group showed an improvement and 8% of the vehicle cream group showed an improvement. Papp et al., (2017) concluded in their study the percent improvement from baseline at week 16 was 83.06% for adalimumab and 80.91% for ABP 501. Papp et al., (2018a) concluded in their study the largest dose of BMS-986165, 12mg daily showed a PASI 75 improvement in 75 % of patients. Papp et al., (2018b) concluded in their study there was significant (*p=<0.001)*

PASI 75, 90, 100 and IGA improvement in all bimekizumab groups as compared to placebo. Warren et al., (2021) concluded in their study Bimekizumab was superior and non-inferior to adalimumab for the primary endpoint PASI 90, 86.2% compared to 47.2%, respectively and IGA score 0/1 at 85.3% compared to 57.2% respectively. Superiority and non-inferiority of bimekizumab versus adalimumab continued through the secondary endpoints.

Summary and Conclusions

Psoriasis is a complex, autoimmune disease that manifests as disease of the skin and joints (Boehncke, 2015). The pathogenesis of psoriasis derives from dysregulation of the adaptive and innate immune system with dendritic cells producing pro-inflammatory cytokines in the exacerbation stage. These cytokines include Tissue Necrosis Factor-alpha (TNF-a) and anti-interleukin 12, 23 and 17 (Boehncke, 2015). Successful use of inhibitors of these cytokines further supports the belief that psoriasis is an immune-mediated disease with genetic and environmental factors (Boehncke, 2015). Manifestations of the disease include plaque, accounting for 90% of all cases, as well as arthritic, guttate, inverse, and pustular (Boehncke, 2015). Because plaque psoriasis accounts for most cases, it's important to examine and synthesize the findings of randomized controlled trials that are used to measure the severity of disease in adults with psoriasis.

This systematic review narrowed down the search results to six randomized, double-blinded studies that compared drug against drug or drug against placebo. These studies were peer-reviewed and all used instruments that measured the severity of disease in adults with psoriasis. The PASI, sPGA and BSA were used commonly for primary endpoints (Studies 1, 3, 4, 5, & 6), however one chose the IGA for their primary endpoint (Study 2). Most studies use the PASI (0 to 72) scale, stating that ≥12 was the threshold for moderate disease (Studies 1, 3, 4, 5 & 6), however one chose to use a modified PASI. The modified PASI created by Lebwohl et al., (2020) substituted anatomical areas 1-9% as fractions rather than whole numbers; according to the authors, this allowed for more precise measurements. Most authors used the term, "moderate" without defining

moderate (Studies 3,4 & 5) instead of using a numeric value for sPGA. Two authors used sPGA scores of ≥3 (Studies 1 & 6). Many authors described how the PASI and sPGA were used to determine the severity of disease (Studies 1, 2, 3, 4 & 6). However, for the sPGA some used a (0 to 4) scale (Study 1), some used a (0 to 6) scale (Study 3) and the others used a (0 to 5) scale, (Studies 4, 5 & 6). Other secondary endpoints were the Psoriasis Symptom Diary score (study 2) and the DLQI score (study 4).

All studies reported outcomes as percent achieved as compared to placebo, comparator formulation or comparator drug (Tables B 1 – 6). Blauvelt et al., (2020) reported achievements in PASI 90 and sPGA 0/1 as primary endpoints, and achievements in PASI 75 & 100, sPGA 0, and DLQI 0/1 as secondary endpoints (Table B - 1). Lebwohl et al., (2020) reported achievements in IGA 0/1 scores as primary endpoints, and achievements in IGA 0/1 plus 2 grade improvement, IGA 0/1, PASI response, PASI 50, 75, 90 and I-NRS as secondary endpoints (Table B - 2). Papp et al., (2017) reported achievement in PASI % improvement from baseline as the primary endpoint and achievement in PASI 50, 90, & 100, and sPGA 0/1 as secondary endpoints (Table B – 3). Papp et al., (2018a) reported achievements in PASI 75 as a primary endpoint and achievements in PASI 50, 90 & 100, sPGA 0/1 and DLQI 0/1 as secondary endpoints (Table B – 4). Papp et al., (2018b) reported achievements in PASI 90 as the primary endpoint and achievements in PASI 75, & 100, and IGA 0/1 as secondary endpoints (Table B – 5). Warren et al., (2021) reported achievements in PASI 90 and IGA 0/1 as primary endpoints and PASI 75, 90 & 100 and IGA 0/1 as secondary endpoints (Table B – 6).

In summary, plaque psoriasis is a systemic inflammatory disease resulting from the dysregulation of the adaptive and innate immune system, manifesting as plaque psoriasis in 90% of all cases (Boehncke, 2015). Using a validated clinical instrument for measuring the severity of disease informs the advanced practice nurse of the optimal therapy and expected achievement in reduction of symptoms.

The findings of this systematic review determined that the PASI, sPGA and BSA are the most used clinically validated instruments used for evaluating the severity of disease in adults with psoriasis.

Recommendations and Implications for Advanced Nursing Practice

Psoriasis is a common disorder with a prevalence in Europe and North America at about 2%, according to the WHO and Boehncke (2015). Encountering adults with psoriasis will not be uncommon in the acute care setting, as psoriasis places patients at greater risk for comorbid conditions (Elmets et al., 2019). Chronic inflammatory diseases, such as psoriasis, are known risk factors for cardiovascular disease. According to Elmets et al. (2019), the incidence of heart disease rises in accordance with the severity of disease. In the general population, heart disease affects 3.58/1000 person-years; in patients with moderate psoriasis this risk increases to 4.04/1000 person-years and for patients affected with severe psoriasis the risk escalates to 5.13/1000 person-years. The authors found that moderate and severe psoriasis are independent risk factors for cardiovascular events and stroke.

The link between a chronic condition such as psoriasis, increasing the risk of a cardiovascular event presents an opportunity for advanced practice nurses in the acute care environment. Many adults living with moderate to severe plaque psoriasis are unaware of their risks associated with psoriasis. Being able to identify and determine the severity of illness using validated instruments allows the advanced practice nurse to inform and provide their patients appropriate referrals and follow-up care.

Dissemination of Findings

This study's findings will be disseminated through the digital commons at Rhode Island College and in a presentation to faculty and students at Rhode Island College.

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Appendix A

Table A-1

Study Specific Data

Blauvelt, A., Leonardi, C. L., Gooderham, M., Papp, K. A., Philipp, S., Wu, J. J., Igarashi, A., Flack, M., Geng, Z., Wu, T., Camez, A., Williams, D., & Langley, R. G. (2020). Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: A Phase 3 randomized clinical trial. *JAMA Dermatology*, *156*(6), 649-658. https://doi.org/10.1001/jamadermatol.2020.0723

Aim/Purpose	Design	Site	Sample	Method	Procedure
The research question is, in adults with moderate to severe psoriasis, is risankizumab efficacious and safe as compared	Double -blind placebo-controlled trial	Multinational, 60 sites in Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, South Korea and the US	507 randomized	Eligible patients older than 18 years old with stable moderate to severe chronic plaque psoriasis for more than 6 months, with or without psoriatic arthritis, body surface area >10%, PASI > or equal to 12, and Static Physicians Global	Part A was a 16-week, double blind treatment, patients were randomized to receive risankizumab, 150 mg or placebo at weeks 0 and 4. At week16 all patients received risankizumab 150 mg. Part

to placebo and continuous treatment vs. withdrawal		Assessment (sPGA) > or equal to 3. PASI ranges from zero (no disease) to 72 (maximal disease) an improvement greater than or equal to 75% is considered clinically meaningful. sPGA ranges from zero (clear) to 4 (severe), Parts A and B were randomly assigned using block randomization, baseline weight, and prior exposure to a tumor necrosis factor alpha inhibitor. The test drug risankizumab was matched to look identical to the placebo.	B began at week 28, patients achieving a sPGA of 0 or 1 were randomly assigned 1:2 to continue risankizumab, 150 mg or placebo (withdrawal of treatment) every 12 weeks. Patients who had sPGA score >2 (inadequate response to therapy) at 28 weeks received open label risankizumab, 150 mg every 12 weeks. Patients initially randomized to placebo achieving sPGA of 0 or 1 were crossed over to receive blinded risankizumab, 150 mg,

every 12 weeks (weeks 28-88). At week 32, initial responders of treatment who relapsed (sPGA score equal to or >3) in part B were retreated with open label risankizumab 150 mg. Final follow-up at week 104

Table A-2

Study Specific Data

Lebwohl, M. G., Papp, K. A., Stein Gold, L., Gooderham, M. J., Kircik, L. H., Draelos, Z. D., Kempers, S. E., Zirwas, M., Smith, K., Osborne, D. W., Trotman, M. L., Navale, L., Merritt, C., Berk, D. R., Welgus, H., & Investigators, A. R. Q. S. (2020). Trial of roflumilast cream for chronic plaque psoriasis. *New England Journal of Medicine*, *383*(3), 229-239. https://doi.org/gh5fpb

Aim/Purpose	Design	Site	Sample	Methods	Procedures
The research question is, in adults with psoriasis, are phosphodiesterase type-4 (PDE-4) inhibitors an effective treatment	Phase 2b, double-blind, randomized controlled trial	30 sites in the US and Canada	332 subjects	Adults 18 years or older with mild, moderate, or severe chronic psoriasis vulgaris, affecting 2 to 20% of BSA, with a severity of 2 or more on a 5-point	332 patients were randomized to 109 assigned to roflumilast cream 0.3%, 113 assigned to roflumilast cream 0.15% and 109 assigned to vehicle cream (placebo). Creams were

for psoriasis in preparations of 0.3% or 0.15% or vehicle cream (placebo)		investigators global assessment (IGA: assessing plaque thickness, scaling, and erythema from zero (clear) to 4 (severe) patients were excluded for areas involving the scalp, palms, and soles. Additionally, the study was limited to 20% with an IGA score of 2 and 15% with an IGA score of 4. Participants	applied once daily for 12 weeks. Primary endpoint was IGA status Secondary endpoints were PASI 50,75 & 90 scores, Worst Itch Numeric Rating Scale (WI-NRS) zero (no itch) 10 (worst itch imaginable), Psoriasis Symptom Diary Score 16 item (zero to 10 scale), and the Dermatology

also were required to have a modified PASI score of at least 2. Randomized in a 1:1:1 to receive either roflumilast 0.03% cream, roflumilast 0.15% cream or placebo. Patients were excluded for above normal exposure to sunlight or tanning beds, an inability to discontinue		Life Quality Index. The original protocol included a modified PASI.

cytochrome P450
inducers or inhibitors,
and those receiving
oral roflumilast or
other PDE-4 inhibitors.

Table A-3

Study Specific Data

Papp, K., Bachelez, H., Costanzo, A., Foley, P., Gooderham, M., Kaur, P., Narbutt, J., Philipp, S., Spelman, L., Weglowska, J., Zhang, N., & Strober, B. (2017). Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *Journal of the American Academy of Dermatology*, *76*(6), 1093-1102. https://doi.org/10.1016/j.jaad.2016.12.014

Aim/Purpose	Design	Site	Sample	Methods	Procedures
The research question aims to determine if ABP501 (a biosimilar to adalimumab) has	Double- blind, randomized controlled trial.	Multicenter	350 subjects	Adults aged 18 to 75 with stable moderate to severe psoriasis for at least 6 months and were candidates for systemic or phototherapy or who were unable to tolerate at	Randomization 1:1 by computer-generation, patients, researchers, and other personnel were blinded. Patients randomized to: ABP 501 with an initial loading

the same efficacy and safety as adalimumab.	least 1 conventional systemic therapy were eligible. Patients needed to have greater than 10% of BSA affected. Patient needed a PASI score of 12 or more. Patients needed an sPGA score of at least moderate severity (6-point scale). Exclusion criteria were active TB, pregnant or having capacity for pregnancy, drug induced psoriasis, non-plaque variants, patients who previously used adalimumab,	dose of 80 mg SQ on week 1 followed by 40 mg SQ on week 2 for 16 weeks, or: adalimumab (no difference in appearance from ABP 501) initial loading dose of 80 mg SQ on week 1 followed by 40mg SQ on week 2 for 16 weeks, Any patient from either arm with a PASI 50 from baseline were eligible to continue in the study and were rerandomized 1:1 to continue

	a comparable biosimilar, or any 2 or more biologics. UV therapy not allowed during trial, upper mid-strength to low potency typical steroids and emollients were ok within 14 days of the first study treatment.	with either ABP 50 or adalimumab or switch.

Table A-4

Study Specific Data

Papp, K., Gordon, K., Thaçi, D., Akimichi, M., Gooderham, M., Foley, P., Girgis, I. G., Kundu, S., Banerjee, S., & Morita, A. (2018). Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *New England Journal of Medicine*, *379*(14), 1313-1321. https://doi.org/10.1056/NEJMoa1806382

Aim/Purpose	Design	Site	Sample	Methods	Procedures
The research question is in adults with psoriasis, are selective inhibitors of tyrosine kinase 2 (TYK2) in doses of 3 mg daily or 3	Double-blind, randomized controlled trial	82 sites in the US, Japan, Poland, Canada, Germany, Latvia, Mexico and Australia	267 subjects	Adults with plaque psoriasis for 6 months or more with a BMI between 18 to 40, who were eligible for UV or systemic therapy and had moderate-severe disease defined by a BSA of 10% or more and a PASI score of 12	Patients were randomly assigned 1:1:1: 1:1:1 to one of 5 doses of a selective TYK2 inhibitor (BSM-986165: 3 mg every other day 3 mg twice daily

mg twice daily or 6mg twice daily or 12 mg daily or placebo effective in treating psoriasis.		or higher and a sPGA score of 3 or higher (0 to 5 scale) Exclusion criteria were a diagnosis of non-plaque psoriasis, currently taking immunosuppressive drugs, history of immune deficiency or Hep B or C, or history of TB or risk of RB, or lack of response to any IL 17 or IL 23 therapy.	6 mg twice daily 12 mg daily Or placebo The primary endpoint was PASI 75 at week 12 Secondary endpoints were PASI 50, PASI 90 and PASI 100, an sPGA score of 0 or 1 and a score of 0 or 1 on the DLQI (0 to 30) BSA was estimated with the handprint method,

one handprint equals 1%

of BSA

Table A-5

Study Specific Data

Papp, K. A., Merola, J. F., Gottlieb, A. B., Griffiths, C. E. M., Cross, N., Peterson, L., Cioffi, C., & Blauvelt, A. (2018). Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12 week randomized, double-blinded, placebo-controlled phase 2b trial. *Journal of the American Academy of Dermatology*, *79*(2), 277-286 e210. https://doi.org/10.1016/j.jaad.2018.03.037

Aim/Purpose	Design	Site	Sample	Methods	Procedures
The research question is in adults with psoriasis does dual neutralization of both interleukin 17 A & 17 F with bimekizumab in	Double-blinded, randomized controlled study	6 countries including Canada, Czech Republic, Hungary, Japan, Poland, and the US	250 subjects	Adults over 18 years with a diagnosis of moderate-to-severe plaque psoriasis for more than 6 months, with a	Patients were randomized in a 1:1:1:1:1:1 computer generated pattern to bimekizumab

doses of 64 mg or 160 mg, or 160 mg plus a 320 mg loading dose, or 320 mg, or 480 mg or placebo injected subcutaneously every 4 weeks improve symptoms of psoriasis	PASI equal to or greater than 12, a BSA equal or greater to 10%, an IGA equal or greater than 3 (0 to 5 scale) who are candidates for UV and systemic therapy. Exclusion criteria include prior anti IL 17 therapy or >1 other biologic	administered every 4 weeks as follows: 64 mg 160 mg 160 mg+320 mg loading dose 320 mg 480 mg And placebo Preparations were prepared off site by unblinded dedicated study personnel

therapy, any significant neuropsychiatric disorder, history of a suicide attempt or suicidal ideation in the past 6 months.	Treatment was administered at baseline, week 4 and week 8. Efficacy and safety were evaluated at weeks 1,2,4,6,8 & 12.

Table A-6

Study Specific Data

Warren, R. B., Blauvelt, A., Bagel, J., Papp, K. A., Yamauchi, P., Armstrong, A., Langley, R. G., Vanvoorden, V., De Cuyper, D., Cioffi, C Peterson, L., Cross, N., & Reich, K. (2021). Bimekizumab versus adalimumab in plaque psoriasis. *New England Journal of Medicine*, *385*(2), 130-141. https://doi.org/10.1056/NEJMoa2102388

Aim/Purpose	Design	Site	Sample	Methods	Procedures
The research question is, in adults with moderate to severe psoriasis is bimekizumab non-inferior to adalimumab in	Double-blind randomized trial of bimekizumab as compared to adalimumab	Multicenter stratified by region: North America, western Europe, central and eastern Europe, or Asia and Australia	478 subjects	Adults older than 18 with moderate-to-severe plaque psoriasis for at least 6 months, PASI at least 12, IGA score at least 3 (0 to 5) scale.	Patients were randomized in a 1:1:1 ratio by use of interactive-response technology to receive: bimekizumab SQ 320 mg every 4 weeks for 56 weeks or:

treating plaque psoriasis	Exclusion criteria were patients previously exposed to bimekizumab or adalimumab, patients that had no response within 12 weeks (primary failure) to any anti-IL 17 biologic agent or to more than one biologic from any class	bimekizumab SQ 320 mg every 4 weeks for 16 weeks, then every 8 for weeks 16 to 56 or: Adalimumab SQ 80 mg at baseline, followed by 40 mg 1 week later and every 2 weeks thereafter until week 24, at this point switched to bimekizumab SQ 320 mg

every 4 weeks to week 56

Injections were administered subcutaneously in the clinic, investigators, other personnel, and the sponsor were blinded. Efficacy and endpoints evaluated by blinded qualified medical professionals.

Appendix B

Table B-1

Outcome Data Collection

Blauvelt, A., Leonardi, C. L., Gooderham, M., Papp, K. A., Philipp, S., Wu, J. J., Igarashi, A., Flack, M., Geng, Z., Wu, T., Camez, A., Williams, D., & Langley, R. G. (2020). Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in Patients with moderate to severe plaque psoriasis: A Phase 3 randomized clinical trial. *JAMA Dermatology*, *156*(6), 649-658. https://doi.org/10.1001/jamadermatol.2020.0723

Variables	Risankizumab	Placebo	Risk difference (95% C), % risankizumab vs placebo	Significance
Part A				
No. of patients per group A	407	100		
PASI 90 at week 16	298 (73.2)	2 (2.0)	70.8 (65.7-76)	*P* <0.001 comparted with placebo

sPGA 0/1 at week 16	340 (83.5)	7 (7.0)	76.5 (70.4-82.5)	*P* <0.001 comparted with placebo
PASI 75 at week 16	361 (88.7)	8 (8.0)	80.6 (74.5-86.6)	*P* <0.001 comparted with placebo
PASI 100 at week 16	192 (47.2)	1 (1.0)	45.5 (40.3-50.8)	*P* <0.001 comparted with placebo
sPGA 0 at week 16	189 (46.4)	1 (1.0)	44.8 (39.5-50)	*P* <0.001 comparted with placebo
DLQI 0/1 at week 16	266 (65.4)	3 (3.0)	62.1 (56.4-67.9)	*P* <0.001 comparted with placebo

Variables				
Part B				
No. of patients per group B	111	225		
sPGA 0/1 at week 52	97 (87.4)	138 (61.3)	25.9 (17.3, 34.6)	*P* <0.001 comparted with risankizumab/placebo
sPGA 0/1 at week 104	90 (87.4)	16 (7.1)	73.9 (66.0, 81.9)	*P* <0.001 comparted with risankizumab/placebo
PASI 75 at week 52	103 (92.8)	161 (71.6)	21.2 (13.7, 28.7)	*P* <0.001 comparted with

				Risankizumab/placebo nominal *p* value
PASI 90 at week 52	95 (85.6)	118 (52.4)	33.1 (24.0, 42.4)	*P* <0.001 comparted with Risankizumab/placebo nominal *p* value
PASI 100 at week 52	71 (64.0)	68 (30.2)	33/7 (23.2, 44.2)	*P* <0.001 comparted with Risankizumab/placebo nominal *p* value

Table B-2

Outcome Data Collection

Lebwohl, M. G., Papp, K. A., Stein Gold, L., Gooderham, M. J., Kircik, L. H., Draelos, Z. D., Kempers, S. E., Zirwas, M., Smith, K., Osborne, D. W., Trotman, M. L., Navale, L., Merritt, C., Berk, D. R., Welgus, H., & Investigators, A. R. Q. S. (2020). Trial of roflumilast cream for chronic plaque psoriasis. *New England Journal of Medicine*, *383*(3), 229-239. https://doi.org/10.1056/NEJMoa2000073

Variables	Roflumilast Cream 0.3% (n=109)	Roflumilast Cream 0.15% (n=113)	Vehicle cream (n=109)	
Primary outcome				
IGA score of 0 or 1 plus at week 6, - % of patients (95% CI)	28 (20 to 37)	23 (16 to 31)	8 (4 to 15)	P = 0.001 and P – 0.004 vs. vehicle group for roflumilast 0.03% and 0.15% respectively

Secondary outcomes				
IGA score of 0 or 1 plus 2-grade improvement at wk. 12, -% of patients (95% CI)	31 (23 to 41)	27 (20 to 36)	14 (8 to 15)	Although sloped in the same direction, no definitive conclusions were made due to the lack of a plan for adjustment for multiple comparisons.
IGA score of 0 or 1, at wk. 12, -% of patients (95% CI)	38 (29 to 47)	32 (20 to 36)	16 (10 to 24)	
IGA score of 0 or 1 plus 2-grade improvement at	94 (67 to 99)	32 (14 to 60)	24 (9 to 50)	

wk. 12 among patients with baseline intertriginous-area IGA score equal or greater than 2, -% of patients (95% CI)			
IGA score of 0 or 1 at wk. 12 among patients with baseline intertriginous-area IGA score equal or greater than 2, -%	95 (69 to 99)	49 (24 to 74)	24 (9 to 50)

of patients (95% CI)			
Least squares mean change in PASI score at wk. 12, -% (95% CI)	-53.2 (-61.1 to 45.2)	-55.0 (-62.8 to -47.2)	-17.0 (-25 to -9.1)
PASI response at wk. 21, -% of patients (95% CI)			
PASI 50	52 (53 to 71)	64 (55 to 73)	24 (17 to 33)
PASI 75	34 (25 to 43)	31 (23 to 40)	16 (10 to 24)
PASI 90	22 (14 to 23)	13 (8 to 21)	7 (4 to 14)
I-NRS response at wk. 12 among patients with	63 (51 to 73)	70 (58 to 80)	33 (22 to 45)

baseline WI-NRS score equal to or greater than 6, -% of patients (95% CI)			
Least-squares mean change in PSD score at wk. 12, (95% CI)	-42.0 (-48.5 to -35.6)	-55.2 (-50.5 to -37.9	-20.9 (-27.3 to -14.5)

Table B-3

Outcome Data Collection

Papp, K., Bachelez, H., Costanzo, A., Foley, P., Gooderham, M., Kaur, P., Narbutt, J., Philipp, S., Spelman, L., Weglowska, J., Zhang, Strober, B. (2017). Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *Journal of the American Academy of Dermatology*, *76*(6), 1093-1102. https://doi.org/10.1016/j.jaad.2016.12.014

Variables	ABP 501	Adalimumab	Sig Level	*P* Value
PASI responders	(n=175)	(n=175)		
PASI % improvement from baseline	80.9	83.1	95% CI fell between -15 to 15 margin demonstrating clinical similarity	
PASI 50 % patient responders	92.4	94.2	0.025	*P*=0.2973

PASI 75 % patient responders	74.4	82.7	0.025	*P*=0.0884
PASI 90 % patient responders	47.1	47.4	0.025	*P*=0.0916
PASI 100 % patient responders	16.9	19.7	0.025	*P*=0.6736
Variables	ABP 501	Adalimumab	Treatment difference	*P* Value
SPGA				
sPGA, clear/almost clear, n/total n (%)	101/172 (58.7)	113/173 (65.3)	-7.4	0.1422
	-18.0 (13.57)	-22.1 (17.11)	1.93	0.0809

Change from

baseline, mean

(SD)

Table B-4

Outcome Data Collection

Papp, K., Gordon, K., Thaçi, D., Akimichi, M., Gooderham, M., Foley, P., Girgis, I. G., Kundu, S., Banerjee, S., & Morita, A. (2018). Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *New England Journal of Medicine*, *379*(14), 1313-1321. https://doi.org/10.1056/NEJMoa1806382

Variables BMS-986165	Placebo (n=45)	3 mg every other day (n=44	3 mg daily (n=44)	3 mg twice daily (n=45)	6mg twice daily (n=45)	12 mg daily (n=44)
PASI 75 primary endpoint						
No. of patients (%)	3 (7)	4 (9)	17 (39)	31 (69)	30 (67)	33 (75)
P value vs. placebo	-	0.49	<0.001	<0.001	<0.001	<0.001
PASI 50						
No. of patients (%)	14 (31)	19 (43)	30 (68)	41 (91)	35 (78)	39 (89)

Difference vs. placebo-percentage points (95& CI)	-	12 (-8 to 32)	37 (18 to 56)	60 (41 to 75)	47 (29 to 65)	58 (41 to 75)
PASI 90 No. of patients (%)	1 (2)	3 (7)	7 (16)	20 (44)	20 (44)	19 (43)
Difference vs. placebo-percentage points (95& CI)	-	5 (-16 to 25)	14 (-7 to 33)	42 (21 to 60)	47 (29 to 65)	41 (20 to 58)
PASI 100 No. of patients (%)	0	1 (2)	0	4 (9)	8 (18)	11 (25)
Difference vs. placebo-percentage points (95& CI)	-	2 (-18 to 23)	-	9 (-13 to 30)	18 (-4 to 38)	25 (4 to 44)

sPGA score 0 orm1 No. of patients (%)	3 (7)	9 (20)	17 (39)	34 (76)	29 (64)	33 (75)
Difference vs. placebo-percentage points (95% CI)	-	14 (-7 to 33)	32 (11 to 50)	69 (51 to 83)	58 (38 to 74)	68 (50 to 82)
DLQI score 0 or 1 No. of patient (%)	2 (4)	7 (16)	7 (16)	19 (42)	27 (60)	28 (64)
Difference vs. placebo-percentage points (95% CI)	-	12 (-2 to 26)	12 (-2 to 26)	38 (20 to 54)	56 (38 to 71)	59 941 to 74)

Table B-5

Outcome Data Collection

Papp, K. A., Merola, J. F., Gottlieb, A. B., Griffiths, C. E. M., Cross, N., Peterson, L., Cioffi, C., & Blauvelt, A. (2018). Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. *Journal of the American Academy of Dermatology*, *79*(2), 277-286 e210. https://doi.org/10.1016/j.jaad.2018.03.037

Variables	Placebo	BZK 64 mg	BZK 160 mg	BZK 160 mg plus 320 mg loading dose	BZK 320 mg	BZK 480 mg	Significance
PASI 75 response % patients wk. 12	4.8	61.5 %	81.4%	85 %	93.0 %	83.7 %	*P* <0.001
PASI 90 response % patients wk. 12	0	46.2 %	67.4 %	75.0 %	79.1 %	72.1 %	*P* <0.001
PASI 100 response % patients wk.12	0	28.2 %	27.0 %	60.0 %	55.8 %	48.8 %	*P* <0.001

IGA 0/1response % patients wk.12	4.8	51.3 %	74.4 %	75.0 %	86.0 %	76.6 %	*P* <0.001

Table B-6

Outcome Data Collection

Warren, R. B., Blauvelt, A., Bagel, J., Papp, K. A., Yamauchi, P., Armstrong, A., Langley, R. G., Vanvoorden, V., De Cuyper, D., Cioffi, C., Peterson, L., Cross, N., & Reich, K. (2021). Bimekizumab versus adalimumab in plaque psoriasis. *New England Journal of Medicine*, *385*(2), 130-141. https://doi.org/10.1056/NEJMoa2102388

Variables	Hypothesis Test in Statistical Hierarchy	Total Bimekizumab (n=319)	Adalimumab (n=159)	Adjusted Risk Difference: Total bimekizumab vs. adalimumab (95% CI) *Percentage points*	Bimekizumab Every 4 WK (n=158)	Adjusted Risk difference: bimekizumab Every 4 WK vs. adalimumab (95% CI)	
		No. (%)	*no. (%)*				
Primary end points							
PASI 90 response at wk. 16	H1 and H3	275 (86.2)	75 (47.2)	39.3 (30.9-47.7)	NA	NA	(95% CI) p<0.001non-inferior and superiority
IGA score of 0/1 at wk. 16	H2 and H4	272 (85.3)	91 (57.2)	28.2 (19.7-36.7)	NA	NA	(95% CI) p<0.001non-

							inferior and superiority
Secondary end points							(95% CI) p<0.001non-inferior and superiority
PASI 100 response at wk. 16	H5	194 (60.8)	38 (23.9)	37.0 (28.6-45.3)	NA	NA	(95% CI) p<0.001non-inferior and superiority
PASI 75 response at wk. 4	H6	244 (76.5)	50 (31.4)	44.8 (36.3-54.4)	NA	NA	(95% CI) p<0.001non-inferior and superiority
PASI 100 response at wk. 24	H7 and H10	213 (66.8)	47 (29.6)	37.1 (28.5-45.7)	107 (67.7)	37.9 (28.1-47.7)	(95% CI) p<0.001non-inferior and superiority
PASI 90 response at wk. 24	H8 and H11	273 (85.6)	82 (51.6)	33.9 (25.4-42.4)	136 (86.1)	34.3 (25.2-43.5)	(95% CI) p<0.001non-inferior and superiority
IGA score 0/1 at wk. 24	H9 and H12	276 (86.5)	92 (57.9)	28.7 (20.2-37.1)	136 (86.1)	28.3 (19.1-37.5)	(95% CI) p<0.001non-

inferior and superiority

H1 & H2 tested non-inferiority of bimekizumab as comparted to adalimumab	H3 & H4 tested the superiority of bimekizumab compared to adalimumab for PASI 90	H7 & H8 & H9 tested the superiority of bimekizumab as compared to adalimumab for PASI 100	H10 & H11 & H12 evaluated the same endpoints on the basis of the group receiving bimekizumab every 4 weeks

Appendix C

Table C-1

Critical Appraisal Skills Progamme

Study 1: Blauvelt, A., Leonardi, C. L., Gooderham, M., Papp, K. A., Philipp, S., Wu, J. J., Igarashi, A., Flack, M., Geng, Z., Wu, T., Camez, A., Williams, D., & Langley, R. G. (2020). Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: A Phase 3 randomized clinical trial. *JAMA Dermatology*, *156*(6), 649-658. https://doi.org/10.1001/jamadermatol.2020.0723

A. Are the results of the trial valid?	**Yes**	**Can't tell**	**No**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		

4. Were patients, health workers, and study personnel "blind" to treatment?	X		
5. Were the groups similar at the start of the trial?			X the study was randomized 4:1
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?	**Yes**	**Can't tell**	**No**
7. How large was the treatment effect?	Part A (73.2%) treatment arm vs (2.0%) placebo achieved PASI 90 Part B treatment arm intention to treat analysis (74% & 83.8%) achieved PASAI 90 and sPGA 0/1 at week 16 vs placebo at (2% & 6.1%)		

8. How precise was the estimate of the treatment effect? $P < 0.001$

C. Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied in your context?	**X**		
10. Were all clinically important outcomes considered?	**X**		
11. Are the benefits worth the harms and costs?	**X**		

Table C-2

Critical Appraisal Skills Progamme

Study 2: Lebwohl, M. G., Papp, K. A., Stein Gold, L., Gooderham, M. J., Kircik, L. H., Draelos, Z. D., Kempers, S. E., Zirwas, M., Smith, K., Osborne, D. W., Trotman, M. L., Navale, L., Merritt, C., Berk, D. R., Welgus, H., & Investigators, A. R. Q. S. (2020). Trial of roflumilast cream for chronic plaque psoriasis. *New England Journal of Medicine*, *383*(3), 229-239. https://doi.org/10.1056/NEJMoa2000073

A. Are the results of the trial valid?	**Yes**	**Can't tell**	**No**
1. Did the trial address a clearly focused issue?	x		
2. Was the assignment of patients to treatments randomized?	x		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4. Were patients, health workers, and study personnel "blind" to treatment?	x		
5. Were the groups similar at the start of the trial?	x		

6. Aside from the experimental intervention, were the groups treated equally?	x		
B. What are the results?	**Yes**	**Can't tell**	**No**
7. How large was the treatment effect?	28% of the roflumilast 0.3% group showed an improvement, 23% of the roflumilast 0.15% group showed an improvement and 8% of the vehicle cream group showed an improvement.		
8. How precise was the estimate of the treatment effect?	P = 0.001 in the 0.3% Roflumilast group P= 0.004 in the 0.15% Roflumilast group		

C. Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied in your context?	x		
10. Were all clinically important outcomes considered?	x		
11. Are the benefits worth the harms and costs?	x		

Table C-3

Critical Appraisal Skills Progamme

Study 3: Papp, K., Bachelez, H., Costanzo, A., Foley, P., Gooderham, M., Kaur, P., Narbutt, J., Philipp, S., Spelman, L., Weglowska, J., Zhang, N., & Strober, B. (2017). Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *Journal of the American Academy of Dermatology, 76*(6), 1093-1102. https://doi.org/10.1016/j.jaad.2016.12.014

A. Are the results of the trial valid?	**Yes**	**Can't tell**	**No**
1. Did the trial address a clearly focused issue?	x		
2. Was the assignment of patients to treatments randomized?	x		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4. Were patients, health workers, and study personnel "blind" to treatment?	x		

5. Were the groups similar at the start of the trial?	x		
6. Aside from the experimental intervention, were the groups treated equally?	x		
B. What are the results?	**Yes**	**Can't tell**	**No**
7. How large was the treatment effect?	The percent improvement from baseline at week 16 was 83.06% for Adalimumab and 80.91% for ABP 501		
8. How precise was the estimate of the treatment effect?	95% CI		
C. Will the results help locally?	**Yes**	**Can't tell**	**No**
9. Can the results be applied in your context?	x		
10. Were all clinically important outcomes considered?	x		
11. Are the benefits worth the harms and costs?	x		

Table C-4

Critical Appraisal Skills Progamme

Study 4: Papp, K., Gordon, K., Thaçi, D., Akimichi, M., Gooderham, M., Foley, P., Girgis, I. G., Kundu, S., Banerjee, S., & Morita, A. (2018). Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *New England Journal of Medicine*, *379*(14), 1313-1321. https://doi.org/10.1056/NEJMoa1806382

A. Are the results of the trial valid?	**Yes**	**Can't tell**	**No**
1. Did the trial address a clearly focused issue?	x		
2. Was the assignment of patients to treatments randomized?	x		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4. Were patients, health workers, and study personnel "blind" to treatment?	x		
5. Were the groups similar at the start of the trial?	x		
6. Aside from the experimental intervention, were the groups treated equally?	x		
B. What are the results?	**Yes**	**Can't tell**	**No**

7. How large was the treatment effect?	The largest dose of BMS-986165, 12mg daily showed a PASI 75 improvement in 75 % of patients.		
8. How precise was the estimate of the treatment effect?	*P* value <0.001 vs placebo		
C. Will the results help locally?	**Yes**	**Can't tell**	**No**
9. Can the results be applied in your context?	x		
10. Were all clinically important outcomes considered?	x		
11. Are the benefits worth the harms and costs?	x		

Table C-5

Critical Appraisal Skills Progamme

Study 5: Papp, K. A., Merola, J. F., Gottlieb, A. B., Griffiths, C. E. M., Cross, N., Peterson, L., Cioffi, C., & Blauvelt, A. (2018). Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. *Journal of the American Academy of Dermatology*, *79*(2), 277-286 e210. https://doi.org/10.1016/j.jaad.2018.03.037

A. Are the results of the trial valid?	**Yes**	**Can't tell**	**No**
1. Did the trial address a clearly focused issue?	**x**		
2. Was the assignment of patients to treatments randomized?	**x**		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	**x**		
4. Were patients, health workers, and study personnel "blind" to treatment?	**x**		
5. Were the groups similar at the start of the trial?	**x**		

6. Aside from the experimental intervention, were the groups treated equally?	**x**		
B. What are the results?	**Yes**	**Can't tell**	**No**
7. How large was the treatment effect?	There was significant (*p=<0.001)* PASI 75, 90, 100 and IGA improvement in all bimekizumab groups as compared to placebo.		
8. How precise was the estimate of the treatment effect?	*P* <0.001		
C. Will the results help locally?	**Yes**	**Can't tell**	**No**
9. Can the results be applied in your context?	**x**		
10. Were all clinically important outcomes considered?	**x**		
11. Are the benefits worth the harms and costs?	**x**		

Table C-6

Critical Appraisal Skills Progamme

Study 6: Warren, R. B., Blauvelt, A., Bagel, J., Papp, K. A., Yamauchi, P., Armstrong, A., Langley, R. G., Vanvoorden, V., De Cuyper, D., Cioffi, C., Peterson, L., Cross, N., & Reich, K. (2021). Bimekizumab versus adalimumab in plaque psoriasis. *New England Journal of Medicine*, *385*(2), 130-141. https://doi.org/10.1056/NEJMoa2102388

A. Are the results of the trial valid?	**Yes**	**Can't tell**	**No**
1. Did the trial address a clearly focused issue?	**x**		
2. Was the assignment of patients to treatments randomized?	**x**		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	**x**		
4. Were patients, health workers, and study personnel "blind" to treatment?	**x**		
5. Were the groups similar at the start of the trial?	**x**		
6. Aside from the experimental intervention, were the groups treated equally?	**x**		
B. What are the results?	**Yes**	**Can't tell**	**No**
7. How large was the treatment effect?	Bimekizumab was superior and non-inferior to adalimumab for the		

	primary endpoint PASI 90, 86.2% comparted to 47.2%, respectively and IGA score 0/1 at 85.3% comparted to 57.2% respectively. Superiority and non-inferiority of Bimekizumab vs adalimumab continued through the secondary endpoints.			
8. How precise was the estimate of the treatment effect?	(95% CI) p<0.001			
C. Will the results help locally?	**Yes**	**Can't tell**	**No**	
9. Can the results be applied in your context?	**x**			
10. Were all clinically important outcomes considered?	**x**			
11. Are the benefits worth the harms and costs?	**x**			

Appendix D

Cross-Study Analysis

Author/Year	Comparisons or Protocol of Study	Primary and Secondary Endpoints	Validated Instruments Used for Evaluating the Severity of Psoriasis	Outcome/Results
Study 1 Blauvelt et al., (2020)	Is risankizumab efficacious and safe as compared to placebo and continuous treatment vs. withdrawal	Primary end points were PASI 90 and sPGA 0/1 improvement at week 16 Secondary end points were PASI 75, PASI 100, sPGA 0, and DLQI 0/1 at week 16	PASI ≥ 12 (0 to 72) scale sPGA ≥ 3 (0 to 4) scale BSA ≥ 10% The authors note that a PASI 75 (or 75% improvement in symptoms) is consider clinically significant. They describe the PASI ranging from 0 (no disease) to 72 (maximal disease) and sPGA ranging from 0 (clear) to 4 (severe)	Part A (73.2%) treatment arm vs (2.0%) placebo achieved PASI 90 Part B treatment arm intention to treat analysis (74% & 83.8%) achieved PASAI 90 and sPGA 0/1 at week 16 vs placebo at (2% & 6.1%)
Study 2 Lebwohl et al., (2020)	Are phosphodiesterase type-4 (PDE-4) inhibitors an effective treatment for psoriasis in preparations of 0.3% or 0.15% or vehicle cream (placebo)	Primary outcome of IGA 0/1 at week 6. Secondary outcomes are IGA 0/1 plus 2-grade improvement at week 12, IGA score 0/1 at week 12, IGA score of 0/1 plus 2-grade among patients with baseline intertriginous-area IGA score equal to or >2,	IGA ≥ 2 (0 to 5) scale Modified PASI ≥ 2 (0 to 72) scale WI-NRS (0 to 10) scale Psoriasis Symptom Diary score (16 item scale) each item (0 to 10) scale The authors note the IGA score ranges from 0 (clear), 1 (almost clear) to 4 (severe) and the modified PASI ranging from 0 (no disease) to 72 (maximal disease)	28% of the roflumilast 0.3% group showed an improvement, 23% of the roflumilast 0.15% group showed an improvement and 8% of the vehicle cream group showed an improvement.

		IGA /01 among patients with baseline intertriginous-area IGA score equal to or >2, PASI response at 12 weeks for PASI 50, 75 and 90 and WI-NRS response at 12 weeks among patients with baseline WI_NRS score equal or >6. Secondary outcomes are reported as point estimates without p values, no clinical inferences can be made.	The authors describe the modified PASI as a tool they developed for measuring, with precision, limited disease. Anatomical areas 1 to 9% are recorded as a fraction rather than a whole number, allowing for derivation from all elements of the PASI score.	
Study 3 Papp et al., (2017)	aims to determine if ABP 501 (a biosimilar to adalimumab) has the same efficacy and safety as adalimumab	Primary efficacy end point was the percent improvement in PASI from baseline to week 16. PASI 50 and PASI 75 responses, sPGA /01. Secondary end points were safety and was assessed monitoring for treatment-emergent adverse events (TEAEs) and serious adverse vents (SAEs), laboratory data, vital sings and immunogenicity.	PASI ≥ 12 (0 to 72) scale sPGA "moderate" (0 to 6) scale BSA ≥10% The authors describe the PASI as "higher scores indicating more severe disease" and sPGA as "ranging from clear to very severe".	The percent improvement from baseline at week 16 was 83.06% for adalimumab and 80.91% for ABP 501

Study 4 Papp et al., (2018a)	are selective inhibitors of tyrosine Kinase 2 (TYK2) in doses of 3mg daily or 3mg twice daily or 6mg twice daily or 12mg daily or placebo effective in treating psoriasis	Primary end point was a 75% or better reduction in the baseline PASI score at week 12. Secondary end points were PASI 50, PASI 90, PASI 100 sPGA 0/1 and DLQI at 12 weeks	PASI ≥ 12 (0 to 72) scale sPGA "moderate" (0 to 5) scale BSA ≥ 10% The authors report that the patient's handprint represents 1% of body surface area They describe the PASI as a summed score of redness, thickness, and scaliness of psoriatic skin lesions, involving the arms, legs, trunk and head, ranging from 0 to 72 with higher scores indication severe disease. They describe the sPGA ranges from 0 (clear) to 5 (very severe disease)	The largest dose of BMS-986165, 12mg daily showed a PASI 75 improvement in 75 % of patients.
Study 5 Papp et al., (2018b)	does dual neutralization of both interleukin 17 A & 17 F with bimekizumab in doses of 64mg or 160mg, or 160mg plus a 320mg loading dose, or 320mg, or 480mg or placebo injected subcutaneously every 4 weeks improve symptoms of psoriasis	Primary efficacy end point was the PASI 90 at week 12. Secondary end points were PASI 90 at week 8, PASI 75 and PASI100 at week 12 and IGA with equal or >2 categories of improvement from baseline at weeks 8 and 12.	PASI ≥ 12 (0 to 72) scale sPGA "moderate" (0 to 5) scale BSA ≥ 10% The authors make no reference describing the clinically validated instruments however, they do define abbreviations used: PASI 75: ≥75% reduction in baseline Psoriasis Area and Severity Index PASI 90: ≥90% reduction in base-line Psoriasis Area and Severity Index	There was significant (*p=<0.001)* PASI 75, 90, 100 and IGA improvement in all bimekizumab groups as compared to placebo.

			PASI100: ≥100% reduction in baseline Psoriasis Area and Severity Index	
Study 6 Warren et al., (2021)	in adults with moderate to severe psoriasis is bimekizumab non-inferior to adalimumab in treating plaque psoriasis	Primary end points were PASI 90 at week 16 and IGA 0/1 with a 2-grade improvement from baseline at week 16. Secondary end points were PASI 100 at week 16, PASI 75 at week 4, PASI 100 at week 24 and IGA 0/1 at week 24. Exploratory end points were DLQI score 0/1at week 25 with PASI 90 and PASI 100 and DLQI score 0/1 at week 56 for patients switched from adalimumab to bimekizumab and did not have a PASI 90 or DLQI 0/1 score at week 24	PASI ≥ 12 (0 to 72) scale IGA ≥ 3 (0 to 5) scale BSA ≥10% The authors state the PASI score ranges from 0 to 72 with higher numbers indicating severe disease They state the IGA ranges from 0 (clear) to 4 (severe disease)	Bimekizumab was superior and non-inferior to adalimumab for the primary endpoint PASI 90, 86.2% comparted to 47.2%, respectively and IGA score 0/1 at 85.3% comparted to 57.2% respectively. Superiority and non-inferiority of bimekizumab vs adalimumab continued through the secondary endpoints.