Sys Rev Pharm 2021;12(2):103-113
A multifaceted review journal in the field of pharmacy

Biological Therapy Of Psoriasis: A Systematic Review Of The Last Decade

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ABSTRACT
Psoriasis has been identified as a chronic disease of the skin in which inflammations are produced, which is impacting 2-3% of population in almost every country around the globe. The study was a systematic review with an objective to figure out the different methods used in the biological therapy and clinical trials of those in the treatment of psoriasis, to study the retrospective analysis of biological therapy for psoriasis in different clinical trials and to compare the results of retrospective analysis of biological therapy for psoriasis with the existing ones. The researcher conducted analysis of 65 studies, which were extracted from a pool of 200 studies taken from different medical databases. The results showed that novel methods of therapies are bearing efficient results and are more effective than previous ones. The results also showed the most to least effective therapies for psoriasis, the most efficient marked was the usage of anti-IL-7 inhibitors (Adalimumab) with 80% of success rate and the least one was the usage of interleukin (IL)-23/Th17, yet with a success rate of 66%. For the purpose of disease prevention, awareness of causes is necessary and for the treatment, awareness of the most reliable and effective method of therapy is necessary. In the current study, both of these have been provided by the researcher, however, the study has its limitations based on the number of studies selected for analysis and the way they were selected.

Keywords: Biological, Therapies, Psoriasis, Disease, Skin, Systematic Review

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INTRODUCTION

Psoriasis is long-lasting skin condition that is characterized by the growth of abnormal skin resulted in red, itchy, scaly and dry patches. It is chronic skin condition that affects almost 2 percent of total population [1]. It can be associated with different health conditions including heart diseases, diabetics, depression and hereditary situation; however, exact reason of psoriasis is not known. Psoriasis appeared on the Egyptian mummies when they were unearthed means it was kept there for thousands for years under the wraps. And the Greeks used the word "psora" meaning "to itch" in ancient ages for psoriasis. All these evidences tell us that this disease is in existence from the centuries. Besides the symptoms which were isolated through ages the most important thing which was hidden from the brilliant minds of medicine of ancient ages was that the disease of psoriasis transfers through DNA and it was doing its work of transferring from generation to generation through ages. In the ancient ages the first work done on psoriasis was done by the Greek "father of medicine" Hippocrates (460-377 B.C.) before his work on the disease it was considered as a curse by the ancient people and he by introducing tar into mix for the treatment of skin ailments replaced the falsehood with knowledge. And he also suggested topical arsenic for the treatment of the disease [2, 3]. Many physicians used toxic materials as a cure for psoriasis. These materials include mercury, sulfur and nitrate they apply these chemicals on the skin of the patients. The benefits of these toxins were lesser than the damages they put to the skin of patient. These solutions were very time-consuming, smelly and irritating. The researcher wonders that what those patients from the ancient ages would have thought of the modern medicines and cures of psoriasis like in Croatia and Turkey the patients are treated with fish therapy fish is used to eat the infected skin of the patient [4].

In these dark eras there are many bright stars who have interjected in the existing knowledge base and worked on finding the cure of the disease. They worked a lot to eliminate the superstitions of the dark age people. This work begun initially in the early 19th century. In the early 19th century the disease was classified as a skin disease according to the course and response to the response to the treatment [5], course, duration, appearance and cause by a doctor named Jean-Louis Albert at a hospital in Paris named Saint-Louis hospital. In the 1840s the founder of modern dermatology Doctor Ferdinand von Herba removed the word "lepra" from the clinical explanation of psoriasis. He was the first who separated psoriasis from "leprosy" forever. After that a century passed and in 1960s for the first time the psoriasis was considered as an autoimmune system and the investigation begun and the researchers identified and introduced it for the first in its own rights as a clinical entity [6].

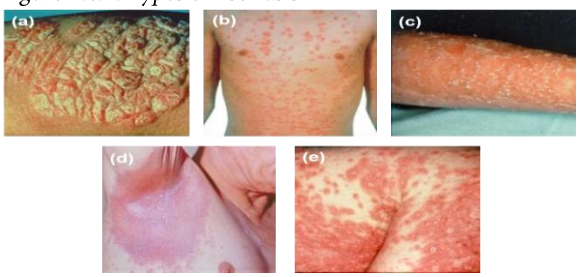
These treatments include phototherapy and laser, topical (skin application-based treatments), and some systematic processes which include (IV medications that suppress the immune system which are oral or injected in skin). In the 1970s since biblical times Israel's dead sea was considered by people as an effective therapy source for its healing properties since biblical times [7]. In the beginning the remedies and the treatments of the disease did not work well for the patients. and with the passage of time the

understanding of the therapists, physicians and doctors has improved this understanding was boosted by the newer technologies [8].

There are large number of possibilities for the generations coming in the future that personalized vaccines can be developed from the immune cells of the carrying patient which can easily emerge with the body of the patient and will stop the psoriasis cells from further growth [9]. The researchers are working hard to eliminate the misconceptions of the society regarding psoriasis and trying to make them believe that it is a disease not a curse. No doubt in the past the remedies were outrageous, and patients were treated inhumanly [10].

One of the most common kinds of psoriasis to be found is Plaque psoriasis, which is characterized with red and raised patched skin which is then enveloped with white cells which are silvery in colour and are dead. These patches can bleed upon cracking and cause itching and pain. These patches can be developed on knees, lower back, elbow and scalp. The second most incident form of psoriasis is known as Guttate psoriasis, that can cause dot like lesions on body by triggering by strep infection. Inverse psoriasis develops in knees and under the arms and is characterized by the red lesions that develop with a shiny and smooth surface. Another type of psoriasis that is common within people is known as Pustular. In this condition blisters of white blood cells surrounded by red skin and can appear on arms and foot. Another form of psoriasis is known as Erythrodermic psoriasis, it is a severe condition but is rarely found in patients. It leads to rigorous redness to develop throughout the body, thus triggering severe pain and itching resulting in loss of skin in the form of sheets. The unstable plaque psoriasis results in erythrodermic psoriasis and occurs in 3 percent of population[11].

Figure No.1: Types of Psoriasis

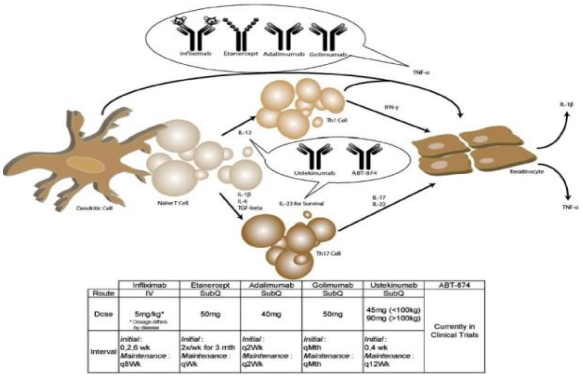


Note: (a) Plaque Psoriasis (b) Guttate Psoriasis (c) Pustular Psoriasis (d) Inverse Psoriasis (e) Erythrodermic Psoriasis

The study of antigens that are involved in auto immune response are not studied till yet though the cytokine secretion of T-cells has been studied and it was found that the pathogenesis of psoriasis occurred by Th1 and Th17 cells. The differentiation of Th1 is initiated by IL-12 while the distinction of Th17 cells is done by IL-1, IL-6 and TGF-α. The vasodilation, leukocyte migration and activation of keratinocytes is resulted by the release of mediator's TNF-α and IFN-α by Th1 cells. This release of mediators results in activation of the dendritic cells, thus causes inflammation [12]. Th-17 cells through the secretion of IL-17 and IL-22 stimulates the initiation and propagation of keratinocyte.

As the antigens can secrete TNF- α that cause inflammation, the anti-TNF biologics etanercept, golimumab, adalimumab and infliximab can neutralize the Th-1 cells and keratinocytes. The antibodies golimumab and adalimumab, that were developed from human, can work against antigen TNF- α. However, the infliximab is derived from mouse anti-TNF antibody that was further humanized for reaction[13]. The linking of TNF- α receptor with Fc portion of an antibody resulted molecularly engineered antibody named as etanercept. The p40 that is subunit of IL-12 and IL-23 is treated by the antibodies ABT-874 and Ustekinumab [14]. The distinction of in the Th-1 cells of the naïve cells is done by IL-12 while IL-23 is used for the creating distinction of Th-17 cells. The secretion of IFN- α from Th-1 cells and IL-17 and IL-22 from Th-17 cells resulted in activation of keratinocytes which results in propagation and excretion of TNF- α and IL-12. The biologics mechanism involved in psoriasis is given in Figure 2.

Figure 1: Mechanism of Biologics in Psoriasis



	Infliximab	Etanercept	Adalimumab	Golimumab	Ustekinumab	ABT-874
Route	IV	SubQ	SubQ	SubQ	SubQ	Currently in Clinical Trials
Dose	5mg/kg*	50mg	40mg	50mg	45mg (<100kg) 90mg (>100kg)	
Interval	Initial: 0,2,6 wk Maintenance: q8Wk	Initial: 2x/wk for 3 mth Maintenance: qWk	Initial: q2Wk Maintenance: q2Wk	Initial: qMth Maintenance: qMth	Initial: 0,4 wk Maintenance: q12Wk	

The innate and adaptive immune response is involved in psoriasis pathogenesis. Alefacept and Efalizumab are considered as primary modulators as T-cells targeting biologics, due to psoriasis, a T-cell mediated disease [15].

The release of anti-microbial peptide LL-37 (cathelicidin) and self-deoxyribonucleic acid (DNA) takes place by the disruption in keratinocytes of epidermis that triggers the psoriasis. The LL-37 forms complex with pathogen derived DNA along with self-DNA [16]. In the dermis, the complex of LL-37 and pathogen derived DNA binds with receptor 9 on plasmacytoid dendritic cell. The stimulation of the dendritic cells take place by the secretion of type 1 interferons (IFN-α and -β), IL-1β and TNF-α from the plasmacytoid dendritic cells results in migration to the lymph nodes through local draining. The complex and migration of cells, upon contacting with native T-cells, trigger the secretion of cytokines, that differentiates the IL-12, IL-23 and TNF-α cells into mature Th17, Th22 and Th1 cells. These T-cells release IL-17A, IL-17F, IL-22, TNF- α and IFN- γ on returning to skin and stimulates the keratinocytes that leads towards proliferation and differentiation [17].

The neutrophils from the circulation of blood are recruited by the chemokines that was secreted by the keratinocytes and ultimately enter the skin and collected by the microbuses of Munro in the epidermis [18]. The TNF- α is produced by the macrophages that are recruited at the place or area where the tenderness, swelling and irritation occurs. The pathological cycle of inflammation, once the cells conscripted at corresponding sites, can activate at specific locations with different triggering factors.

Despite the previous findings found on the biological therapy carried out for the therapy of psoriasis, it is still a problem that the clinical trials of most drugs have not been done. Moreover, some antibodies developed for the biological therapy of psoriasis only migrated the cells but actual targeting of cell is not developed [11]. For this, different researches have been developed to relate the treatment of psoriasis with biological therapies or altercations.

Through reference taken from the past studies and research papers, it is found that different antibodies that have been established for the therapy of psoriasis. Moreover, there is a data available related to the development of different biologics for psoriasis treatment but only few researchers investigated the effects of these biologics on clinical trials. However, the systematic review for the biological remediesforPsoriasis has not been considered in the past and thus in the current study, the researcher has aimed to conduct a systematic review on the domain. The objectives of the present study thus are to figure out the different biologics used in the biologic therapy and clinical trials of those in treatment of psoriasis, to study the retrospective analysis of biology therapy for psoriasis in different clinical trials, to evaluate the findings of different studies on biological psoriasis.

METHODOLOGY

The first step of this systematic review was to collect data regarding the relevant chosen topic. The preferred formats for the data included was research articles, research papers, past clinical studies conducted and thesis involving the empirical data about the relevant topic. So, for the purpose of data searching and collection, PubMed, Wiley online library, Elsevier were used. The key words of "Biological therapy of Psoriasis" were used and as a result of searching multiple times, a mixture of about 200 articles, papers and detailed studies was obtained. The time duration that was selected, ranged from 2010 to 2020, the search and collection was limited to the English language only because the resultant required was going to be in English as well. After the collection of 200 articles, the next step was to short list them, in order to work on the most relevant and closest studies to the selected topic. For the purpose of shortlisting, the abstracts of all of the articles, papers and detailed studies were taken as a standard and then the abstracts were fully read and understood in order to know about the theme of the studies. From the abstracts, the objectives of the studies were compared, the studies who' objectives matched with the current study were shortlisted and taken while the one's having different objectives were discarded. After all of the screening processes, out of 200 results, only 65 articles and research papers were selected which included, "[19], [20], [21], [22], [23], [24], [25], [26], [27] and [28]." Published by, "Medical Journals Limited, JAMA Network, Indian Journal of Dermatology, Dove Medical Press Limited, Springer, Wiley Online Library, British pharmacological society"

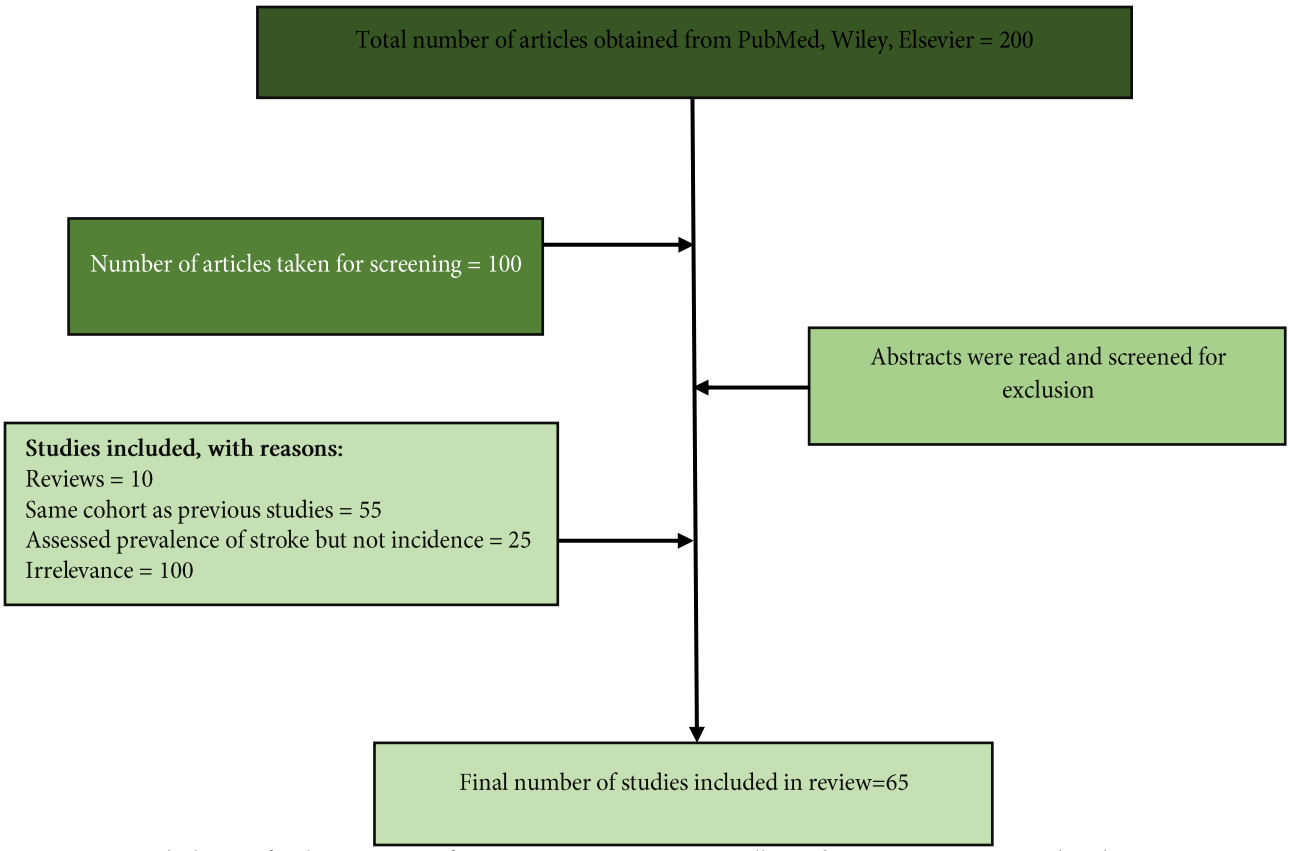
From the papers and the articles selected, the data about the setting of the study was collected for each of the article selected, the details of study designs were recorded, the data of the number of received cases and the details of control group were recorded, age of the patients, sex of the patients, the statistical adjustments for the comorbidities, data collection processes, nature of the data and severity of psoriasis assessed were all recorded for the next steps. The following figure No.3 represents the selection criteria of the studies.

REVIEW

Psoriasis

Psoriasis is defined as a skin disease that has been labelled to be chronic. It usually results from the dysregulation between the keratinocytes and the immune cells that infiltrate. The reporting is done based on a psoriasis disease model, which is prompted by the transmission of $CD4^{+}CD45RB^{hi}CD25^{-}$ cells to pathogen-free *scid/scid* mice. Neutralization of IL-22 has prohibited from the progress of the disease, which is known for decreasing acanthosis (thickening of the skin), which is infiltration of the inflammatory, and is an manifestation of Th17 cytokines [29]. The direct indulgence of the IL-22 onto the skin glands of the healthy mice prompted proinflammatory cytokine gene expression and the antimicrobial peptides. The data for the study suggests that IL-22, which is resultant on the nonhematopoietic cells and the keratinocytes, is an essential requirement for the development of the reaction of Th17 cell–dependent disease, studied through the current model of inflammation in the skin. The main proposition thus formulated is that antagonism of IL-22 could be a possibly favourable therapy for the treatment of psoriasis in humans[30]. The regulation of T- cells functions i.e. TAGAP, STAT3 and RUNX3 by targeting with candidate genes of autoimmune diseases with newly identified loci. The products that were involved in host defense mechanism included nuclear factor (NF)-κB signaling (*CARD14* and *CARM1),* macrophage activation *(ZC3H12C)* and interferon-mediated antiviral responses *(DDX58).* The results of this systematic review showed the significance of skin in naïve and learnt host defense mechanism by understanding the distinctive and shared the factors of the inflammatory disorders mediated through the immune system[31].

Figure No. 3: Selection Criteria



Conventional Therapy for the treatment of Psoriasis

A new model that described the complex interactions of patient, treatment characteristics, behavior of adherence, disease and treatment outcomes is developed by the International Psoriasis Council Topical Therapy Working Group. The adherent behavior in different patients is encouraged by providing the recommendations that help in assistance of health care provider [32, 33]. The treatment guidelines recommend these biologics as third line therapies, although showed tolerability and good efficacy in trials, due to lack of safety data for long term use. The meta-analysis and open label extension studies and controlled trials data of efalizumab, Ustekinumab, adalimumab, etanercept, alefacept and infliximab showed the safety data which can be used for the medication of severe to moderateplaque psoriasis. These all biologics are considered as long term studies and as an alternative for conventional non-biologic agents that have been used for the therapy of severe to moderate treatment of plaque psoriasis except efalizumab that has been banned form U.S. and European market [34].

Emergence of Biological Therapy in treatment of Psoriasis

For years psoriasis has been thought to be disease in skin which is the function of abnormal behavior of keratinocytes [35]. But more evidences provided by the researchers have geathered the world on the fact that in both maintaining and initiating the psoriasis, immune system of human body plays a vital role. The study made on four patients by Mueller and Hermann in 1979 so that they can investigate the effect put on the rheumatoid arthritis by the ciclosporin. They were surprised when they came to know that on psoriasis skin lesions the effect of ciclosporin is excellent. As part of the mechanism the effect of ciclosporins anti-lymphocytic on T-cells has been discussed by their study. In cases where the topical agents appeared to ineffective and inefficient along with other small molecules a small molecular drug ciclosporin was introduced for the treatment of psoriasis. The terms biologic, biological, biopharmaceutical [36], bioproducts and biological therapy are used randomly, but in actual these terms comprise a large number of products having natural origin for example; recombinant protein sources, gene therapy, blood components and blood and vaccines. On the other hand, in today's world including receptor fusion proteins and monoclonal antibodies the complex molecules which represent the targeted therapy are referred to as the subgroups of the large by the researchers [37]. This study will use the word biologic. In comparison to the smaller molecules the biologics are the larger ones.

On biologics for psoriasis there is no specific definition that can clearly define them as new or old therapy. But on the other hand, the target of the oldest group of biological therapies was the migration and activation of efalizumab, alefacept and T-cells [38]. So those biologics are referred to as

first generation biologics which target TNF-α. These are adalimumab, infliximab and etanercept. Biologics are not like other drugs these actually target the specific part of the human immune system. A specific type of cell which is involved in the psoriasis called T-cell biologics basically block its actions. The protein in the immune system is also blocked by the biologics [39].

For children having severe psoriasis biologics have appeared to be very effective. The therapists prescribed biologics for the treatment of children with psoriasis. For the people of age 12 year and older Ustekinumab has been approved by the FDA for the treatment of moderate-severe psoriasis. In addition to all these factors effectiveness and safety are also important to be considered during the therapy [40]. If we discuss safety, then in general biologics possess a good record regarding safety. In case of biologics the issue of biggest concern is of the development of a serious infection in the patient. In order to avoid this problem before prescribing a biologic the dermatologists screen each patient carefully. For the purpose of safety, before prescribing a biologic for the treatment of psoriasis the patient is required to have a medical test by the dermatologists. Mainly the tests of tuberculosis and some other blood tests are required [41]. Depending on the condition and extent of the disease specific patients are required to have few additional medical tests. In order to discuss the effectiveness of the biologics the previous studies have shown that for the treatment of psoriatic arthritis and psoriasis biologics appeared to be very effective. Biologics may appear to be most effective for the treatment of moderate to severe psoriasis in many cases. The effectiveness of the biologic comes with continuity of doses. A person will get greater results if he will take biologics regularly as compared to someone who does not take the doses properly [42]. The gaps in the doses of the biologics will result in some side effects as well as the biologic will lose its effect on the immune system.

In a case where a biologic has lost its effect as a result of discontinuity in doses or after some time another biologic may work. However, for some people a biologic may lose its effect after using it for some time, but studies have shown that its effectiveness remains active for some people for the course of years [42]. It is said that "nothing is perfect" same is the case with biologics. There are many possible side effects depending on the nature and kind of each biologic. These side effects vary from biologic to biologic. Some of these side effects are of mild nature and they do not force patients to stop their regular treatment. The most common side effects can be the headache, the urinary tract infection is also very common, many patients are observed to have flu like symptoms, in the same way many patients faced skin reaction on the place where the therapist injected the biologic, in addition to all these side effects patients also suffered the upper respiratory tract infection [43]. As this is known that by calming down the part of the immune system the biologics cast their effect. People taking biologics can develop serious other infections because their immune system does not remain as effective over the course of therapy as it was before starting the therapy. Patients having a history of infections, or those who chew or smoke tobacco as well as the patients having diabetes have higher chances of getting infected during the course of therapy [44]. Patients with age over 55 years also have higher chances of getting infected. The dermatologists who have patients under their supervisions watch their patients regularly for the signs of infections and problems regularly so these problems can be controlled or stopped by taking precautionary measures.

The patient will be required to take fewer medical tests when he has to take some other strong psoriasis medicine like methotrexate or cyclosporine as compared to the patient who is going to take some biologics. Before taking any biologics, the patient must discuss some facts with his or her dermatologists. The patient must tell her dermatologist if she is pregnant, he/she must ask the dermatologist about the application or usage of the biologic that how it will be used, the patient must tell his/her dermatologist if he/she has stopped taking the biologic, in addition to all these things the patient must discuss with his/her dermatologist if he/she observe any side effects of the biologic during its usage [45]. This was the evolution of the biologics. The that has been already done in the field of biologics is revolutionary and what must be done in the coming ages is plentiful.

Non-cytokine Biologics

A non-cytokine biologic, alefacept was considered to impede the interaction of CD2/LFA-3 that is important for the functioning of T-cell. For this, different clinical trials were done for measuring the efficiency of alefacept in the therapy and treatment of psoriasis and it was found that clinical trials of IV or IM alefacept proves to be operative in the management of psoriasis. The clinical trials for measuring the efficacy of biologic were done for 12 weeks and the primary point for improvement was considered as 2 weeks with the maintenance of efficacy at 12 weeks. It was found in one study that without having any effect on the naïve T-cells, alefacept reduced the memory effector T-cells [46]. Another study demonstrated that two courses of alefacept had more efficacy as contrasted to the withdrawal of placebo or crossover cohorts.

A meta-analysis was done for determining the effects of alefacept on the patients that used it for treatment of psoriasis. It was found by meta-analysis that about 9% risk was present having adverse effects on the alefacept treated patients. The nausea, pharyngitis, dizziness, headache, pruritus and infusion-related chills were considered as adverse effects of alefacept on patients. A meta-analysis carried for the evaluation of the safety of alefacept, resulted that the cellulitis in three subjects, myocardial infarction in three subjects and coronary artery disease in four subjects, however, in placebo groups no adverse effect was found. The adverse effect of IV dosing was observed over the IM

dosing. The alefacept was administrated by IM by the anti-alefacept antibodies of 4 percent studies. The non-neutralization was done by the antibodies and there was no adverse effects were found by the use of antibodies [47].

Cytokine Biologics

The efficacy of infliximab was determined by different clinical trials and it was found that the efficacy of IV infliximab was PASI 75 at 75-88% in 10 weeks having dosage of 5 mg/kg as compared to 1.9-6% at the placebo. It was studied that dosage of 3 mg/kg as intermediate is effective to achieve PASI 75 with70-72% at 10 weeks. The effectiveness of the biologic was upheld for 46-50 weeks with loss in response at anti-infliximab antibodies. Another study demonstrated the 6 percent worsening and 26 percent progress in the psoriasis of the nailsmoderated through infliximab and placebo treatments. The rhinitis, sinusitis, headache and transaminitis are common effects of infliximab [48].

The side effects observed in the adults by this dosage were headaches, respiratory tract infections, injection site reactions and sinusitis. During the initial3 months of therapy with approached placebo levels, there was more observance of injection site reactions. Moreover, the streptococcal pharyngitis and skin papilloma's were observed as side effects of biologic in pediatric study [49] .

Similarly, in contrast to the placebo in phase 2 and phase 3 trials, subcutaneously injected adalimumab was considered as an effective for achieving PASI 75. The increased adalimumab dose was compared against the placebo dose to observe the dose response in phase 2 study. It was found in 12th week of therapy that PASI 75 was achieved in 4 percent, 53 percent and 80 percent by the dosage of 40 mg every other week and 40 mg weekly. It was also found in phase 3 study that a PASI 75 was achieved by 40 mg dosage with 71 – 79% subjects or patients as compared to 7 -18% subjects in placebo group of 16 weeks treatment. The higher efficacy rate for achieving PASI 75 was found in placebo groups of phase 3 studies in relation to 12 weeks treatment in phase 2 study. The correlation of antibodies with loss of response was found by developing of antibodies in 8.8 percent patients against adalimumab at some stage of their treatment against psoriasis [50].

Clinical Trials of Different Biologics in the treatment of Psoriasis

A large amount of cytokine that is associated with inflammation, tumor necrosis factor (TNF) is produced by the inflammatory cells and keratinocytes in inflamed skin. For the therapy of the skin diseases persistent through inflammation, monoclonal anti TNF- α can be used that blocked the proinflammatory cytokine. The efficacy of anti TNF- α antibody that is infliximab was determined for the therapy of skin lesions of psoriatic arthritis. For this, six patients having skin lesions persistent through psoriasis and joint disease were treated with anti TNF- α antibody as they were unresponsive to methotrexate therapy for the treatment [13]. The psoriasis area and the index were determined before and after the 10 weeks of therapy. It was observed in the patients that the patient's conditions having psoriatic skin lesions got improved and improvement of joint disease was also observed. It was concluded by this study that the use of anti-TNF- α antibody is an effective therapy treatment for the treatment of psoriatic skin lesions and psoriatic arthritis [51].

Another study demonstrated the clinical trials that showed the improvement in physical and health related quality of life (HRQoL) to treat the psoriasis with biologic therapy as compared to the placebo treatment. However, only a limited interpretation of Dermatology Life Quality Index (DLQI) was found by this study that provides limited data for comparison. For this, the biological therapy was found for the treatment of patients having chronic plaque psoriasis that provides the visible improvement in quality of life and accessed by the Dermatology Life Quality Index (DLQI). Different researches of this study review the data of some biologics (efalizumab, infliximab, alefacept and etanercept) currently used for the treatment of chronic plaque psoriasis [52].

The infliximab treated patients achieved PASI 90 with dosage of 5 mg/kg and 3 mg/kg having 75% and 70% patients at week 10. PASI responses was maintained with continuous therapy as compared to intermittent therapy through week 50 and for 5 mg.kg was compared with 3 mg/kg. It was concluded that infliximab was more effective in treating the psoriasis [53]. Another study shows that the role of Th17 in addition to Th1 cells for the pathogenesis of the psoriasis. The Th17 cells have been recognized to be essentially important in configuring the activation of the epidermal of the plaques in psoriasis, in contrast to the Th1 cells, which should also be removed for resolution of the disease[54].

Superiority of Adalimumab over Methotrexate

The treatment of psoriasis with adalimumab against methotrexate was compared in phase 3 studies. It was found that about 35 percent and 79 percent subjects achieved PASI 75 by methotrexate and adalimumab treatment groups respectively at 16 weeks [55]. The side effects of adalimumab treatment observed were nasopharyngitis, cellulitis, headache and upper respiratory infections. For moderate to severe psoriasis the treatments options generally require a systematic approach towards medication [56]. Although the individual's systematic agent's mechanism of action relative to placebo, efficacy and safety has also been evaluated by a number of reports these reports have also been evaluated the comparison between different systematic agents that which agent is appeared to be more effective.

FINDINGS

The researcher has collected the data from the sixty five selected studies and after that, statistical analysis has been performed on the collected data. After recording the number of patients present in each study, the mean ages of the patients were calculated and recorded, the researcher

has added the mean values of percentage of males taken as a sample in the study and the remaining numbers present the female population taken as a sample. The researcher has also calculated the BMI or body mass indexes for all of the patients taken from the ten selected studies. As far as the past medical record is concerned, the researcher has taken out the data for diabetes mellitus, skin cancer and other kinds of cancers present in the studies and has reported the cases of those in simple numbers. The p values were also calculated. The researcher has focused on the success rates of all kinds of treatments used because it fulfils the primary objective and aim of the study to compare the different biological treatments for psoriasis, with these figures, it can be fairly decided that which kind of treatment can be fairly recommended to be used for the treatment of psoriasis.

Table No1= Treatment methods

No.	Title	Year	Country	Design	Psoriasis Type	Treatment method under study
1	Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases	2016	Poland	Retrospective	Plaque psoriasis	Usage of anti-IL-7 inhibitors (Secukinumab (AIN457))
2	Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents	2010	Austria	Prospective	Psoriatic arthritis	Usage of anti-IL-7 inhibitors
3	Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomized double blind multicenter trial	2010	Europe, Latin America, and the Asia Pacific region.	Retrospective	Active psoriasis and psoriatic arthritis	Usage of etanercept 50 mg
4	Biological therapy of psoriasis	2010	California	Retrospective	Psoriatic arthritis	Usage of ustekinumab
5	TARGETING IL-23: insights into the pathogenesis and the treatment of psoriasis	2010	Brazil, USA	Prospective	Psoriatic arthritis and plaque psoriasis	Usage of IL-23
6	Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis	2014	USA	Retrospective	Psoriatic arthritis	Usage of anti-TNF-α agents
7	Systemic Combination Treatment for Psoriasis: A Review	2010	Denmark	Retrospective	Psoriasis	Usage of retinoid and phototherapy
8	Cytokine-Based Therapy in Psoriasis	2012	Canada	Prospective	Psoriasis	Usage of interleukin (IL)-23/Th17 axis
9	Risk of Serious Infection with Biologic and Systemic treatment of psoriasis	2015	USA	Prospective	Psoriasis	Usage of ustekinumab, infliximab, adalimumab, etanercept
10	Obesity and psoriasis: body weight and body mass index influence the response to biological treatment	2011	Spain	Retrospective	Psoriasis	Usage of adalimumab, etanercept, infliximab and ustekinumab.

Comparison of biological therapies of Psoriasis

Table No.2: Comparison of biological therapies of Psoriasis

No.	Psoriasis Type	Treatment method under study	No. of patients	Success rate	Adverse Effects
1	Plaque psoriasis	Usage of anti-IL-7 inhibitors (Secukinumab (AIN457))	2044	75.90%	Nasopharyngitis, headache, nausea, dizziness, fatigue and diarrhea

2	Psoriatic arthritis	Usage of anti-IL-7 inhibitors (Adalimumab)	50	80.00%	Injection site reactions, headache
3	Active psoriasis and psoriatic arthritis	Usage of etanercept 50 mg	752	75%	Serious infections
4	Psoriatic arthritis	Usage of ustekinumab	650	68%	Dizziness, nausea, infusion-related chills, pharyngitis, headache and pruritus
5	Psoriatic arthritis and plaque psoriasis	Usage of IL-23	85	77%	Dizziness, nausea and headache
6	Psoriatic arthritis	Usage of anti-TNF-α agents	652	76%	Severe infections and nausea
7	Psoriasis	Usage of retinoid and phototherapy	530	75.22%	Headache, nausea and dizziness
8	Psoriasis	Usage of interleukin (IL)-23/Th17 axis	102	66%	Emergence of lesions and infections
9	Psoriasis	Usage of ustekinumab, infliximab, adalimumab, etanercept	11466	69.05%	Pneumonia and cellulitis
10	Psoriasis	Usage of adalimumab, etanercept, infliximab and ustekinumab	246	72%	Headache, fatigue and dizziness

Table number 2 above is a representation of a comparison between the different novel ways of therapies for different kinds of psoriasis. It was seen that the usage of anti-IL-7 inhibitors (Secukinumab (AIN457)) resulted in 75.90% of success rate in therapy [57] and its adverse impacts included nasopharyngitis, headache, nausea, dizziness, fatigue and diarrhea. The usage of anti-IL-7 inhibitors (Adalimumab) resulted in 80.00% of success rate in therapy and its adverse impacts included injection site reactions and headache [58]. The usage of etanercept 50 mg resulted in 75% of success rate in therapy and its adverse impacts included serious infections of the site [59]. The usage of ustekinumab resulted in 68% of success rate in therapy and its adverse impacts included dizziness, nausea, infusion-related chills, pharyngitis, headache and pruritus [60]. While, the usage of IL-23 resulted in 77% of success rate in therapy and its adverse impacts included dizziness, nausea and headache. The usage of anti-TNF-α agents resulted in 76% of success rate in therapy and its adverse impacts included severe infections and nausea. The usage of retinoid and phototherapy resulted in 75.22% of success rate in therapy and its adverse impacts included headache, nausea and dizziness [61]. The Usage of interleukin (IL)-23/Th17, resulted in 66% of success rate in therapy and its adverse impacts included emergence of lesions and infections. The usage of ustekinumab, infliximab, adalimumab, etanercept resulted in 69.05% of success rate in therapy and its adverse impacts included Pneumonia and cellulitis incurrence. And the usage of adalimumab, etanercept, infliximab and ustekinumab resulted in 72% of success rate in therapy and its adverse impacts included headache, fatigue and dizziness. It can be seen that nausea, headache and dizziness are common as a result of most of the therapies, whereas, the novel methods have shown higher success rates as compared to the previous ones.

DISCUSSION

The most efficient way to treat psoriasis according to the success rate reported is the way with the usage of anti-IL-7 inhibitors (Adalimumab), on second comes the way with the usage of IL-23 [62], by success rate, the third one is by the usage of anti-TNF-α agents, fourth efficient one is the usage of anti-IL-7 inhibitors (Secukinumab (AIN457)), fifth one is retinoid and phototherapy, sixth one is usage of etanercept 50 mg [63], at the seventh place is the usage of ustekinumab, infliximab, adalimumab and etanercept [64], at the eighth place is the usage of ustekinumab and at the last place in efficiency of treatment, according to the success rate of the novel methods of therapies of psoriasis comes the treatment with the usage of interleukin (IL)-23/Th17 [65]. The current study has enlisted the most efficient ways of therapies used in the modern era for the treatment of psoriasis, the study has also given a comparison based on the success rates and it was seen that both the prospective and retrospective studies have provided sufficient amount of evidences to prove the efficiency or inefficiency of the novel methods used [66].

CONCLUSION

The study was a systematic review with an objective to figure out the different biologics used in the biologic therapy and clinical trials of those in treatment of psoriasis, to study the retrospective analysis of biology therapy for psoriasis in different clinical trials and to compare the results of retrospective analysis of biology therapy for psoriasis with the existing ones. The study conducted analysis of 65 studies, which were extracted from a pool of 200 studies taken from PubMed, Wiley, Elsevier etc. The

findings showed that novel methods of therapies are bearing efficient results and are more effective than previous ones. The results also showed the most to least effective therapies for psoriasis, the most efficient marked was the usage of anti-IL-7 inhibitors (Adalimumab) with 80% of success rate and the least one was the usage of interleukin (IL)-23/Th17, yet with a success rate of 66%.

Implications of the study

Psoriasis is a chronic and inflammatory disease of skin, which is impacting 2-3% of population in almost every country around the globe. For the purpose of disease prevention, awareness of causes is necessary and for the treatment, awareness of the most reliable and effective method of therapy is necessary. In the current study, both of these have been provided by the researcher as a crux of 65 of the best researches done on the therapies of psoriasis. The study has provided a crux of the best novel methods being used around the globe in order to treat different conditions of psoriasis, so that after going through the results mentioned, it can better be decided by different individuals that which therapy or method one should go with. Moreover, as the comparison is provided, the selection of the therapy can become easier as well.

Limitations of the study and future research recommendations

The current study is a novel and valuable addition in the previous studies conducted as a systematic review on the therapies of psoriasis. But it has its own limitations as well. The researcher has collected only 200 studies out of which only 65 were used to conduct the systematic review. The number is too low to call the results valid and generalizable. The future researchers are recommended to collect at least 500 studies out of which at least 250 will be used for the purpose of conducting analysis. The researcher has generalized the results globally while, the studies have been selected randomly, future researchers are recommended to collect studies regarding the therapies of psoriasis from at least 15 different countries so that the results can be considered valid with a global perspective.

REFERENCES

1. Raychaudhuri, S.P. and E. Farber. (2001). The prevalence of psoriasis in the world. Journal of the European Academy of Dermatology and Venereology, 15(1), 16-17. https://doi.org/10.1046/j.1468-3083.2001.00192.x
2. Ziaei, S.M. (2015). Effects of financial development indicators on energy consumption and CO2 emission of European, East Asian and Oceania countries. Renewable and Sustainable Energy Reviews, 42, 752-759.https://doi.org/10.1016/j.rser.2014.10.085
3. Zhang, J. (2018). Cross-border E-commerce Development Strategy Under the" Internet+ Logistics Finance" Model.https://doi.org/10.1016/j.jclepro.2017.03.203
4. Zhang, B., B. Wang, and Z. Wang. (2017). Role of renewable energy and non-renewable energy consumption on EKC: evidence from Pakistan. Journal of Cleaner Production, 156, 855-864.
5. Zahoor, H., et al. (2015). A research framework for investigating the relationship between safety climate and safety performance in the construction of multi-storey buildings in Pakistan. Procedia engineering, 118, 581-589.https://doi.org/10.1016/j.proeng.2015.08.488
6. Zahid, M. and G. Rasul. (2012). Changing trends of thermal extremes in Pakistan. Climatic change, 113(3-4), 883-896.https://doi.org/10.1007/s10584-011-0390-4
7. Zahid, M. and G. Rasul. (2011). Frequency of extreme temperature and precipitation events in Pakistan 1965–2009. Science International, 23(4), 313-319.https://hdl.handle.net/20.500.12432/988
8. Yukhanaev, A., S. Sharma, and A. Nevidimova. (2014). Subnational determinants of foreign direct investments in the Russian Federation. Journal of Eastern European and Central Asian Research (JEECAR), 1(2), 10-10.
9. Yücel, İ. (2012). Examining the relationships among job satisfaction, organizational commitment, and turnover intention: An empirical study.
10. Yousuf, I., et al. (2014). Carbon emissions from power sector in Pakistan and opportunities to mitigate those. Renewable and Sustainable Energy Reviews, 34, 71-77.https://doi.org/10.1016/j.rser.2014.03.003
11. Swanbeck, G., et al. (1995). Age at onset and different types of psoriasis. British journal of dermatology, 133(5), 768-773.https://doi.org/10.1111/j.1365-2133.1995.tb02753.x
12. Raychaudhuri, S.P. and J. Gross. (2000). A comparative study of pediatric onset psoriasis with adult onset psoriasis. Pediatric dermatology, 17(3), 174-178.https://doi.org/10.1046/j.1525-1470.2000.01746.x
13. Zaba, L.C., et al. (2007). Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. Journal of Experimental Medicine, 204(13), 3183-3194.10.1084/jem.20071094071408c
14. Kimball, A.B., et al. (2008). Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. Archives of dermatology, 144(2), 200-207.https://doi.org/10.1111/j.1365-2133.2004.06093.x

15. Sampogna, F., et al. (2004). Prevalence of symptoms experienced by patients with different clinical types of psoriasis. British Journal of Dermatology, 151(3), 594-599.https://doi.org/10.1016/S0190-9622(85)70188-0
16. Henseler, T. and E. Christophers. (1985). Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. Journal of the American Academy of Dermatology, 13(3), 450-456.https://doi.org/10.1038/nature05663
17. Lowes, M.A., A.M. Bowcock, and J.G. Krueger. (2007). Pathogenesis and therapy of psoriasis. Nature, 445(7130), 866.
18. Griffiths, C.E. and J.N. Barker. (2007). Pathogenesis and clinical features of psoriasis. The Lancet, 370(9583), 263-271.https://doi.org/10.1016/S0140-6736(07)61128-3
19. Weger, W. (2010). Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents. British journal of pharmacology, 160(4), 810-820.https://doi.org/10.1111/j.1476-5381.2010.00702.x
20. Wasilewska, A., et al. (2016). Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii, 33(4), 247.doi: https://doi.org/10.1136/bmj.c147
21. Sterry, W., et al. (2010). Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Bmj, 340, c147.
22. Sivamani, R.K., et al. (2010). Biological therapy of psoriasis. Indian journal of dermatology, 55(2), 161.doi: 10.4103/0019-5154.62754
23. Puig, L. (2011). Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. Journal of the European Academy of Dermatology and Venereology, 25(9), 1007-1011.https://doi.org/10.1111/j.1468-3083.2011.04065.x
24. Mitra, A., R.S. Fallen, and H.C. Lima. (2013). Cytokine-based therapy in psoriasis. Clinical reviews in allergy & immunology, 44(2), 173-182.
25. Lima, H.C. and A.B. Kimball. (2010). Targeting IL-23: insights into the pathogenesis and the treatment of psoriasis. Indian journal of dermatology, 55(2), 171.doi: 10.4103/0019-5154.62760
26. Kivelevitch, D., B. Mansouri, and A. Menter. (2014). Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis. Biologics: targets & therapy, 8, 169.
27. Kalb, R.E., et al. (2015). Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA dermatology, 151(9), 961-969.doi:10.1001/jamadermatol.2015.0718
28. Jensen, P., L. Skov, and C. Zachariae. (2010). Systemic combination treatment for psoriasis: a review. Acta dermato-venereologica, 90(4), 341-349.https://doi.org/10.2340/00015555-0905
29. Greaves, M.W. and G.D. Weinstein. (1995). Treatment of psoriasis. New England Journal of Medicine, 332(9), 581-589.
30. Raychaudhuri, S.P., et al. (2008). FR255734, a humanized, Fc-Silent, Anti-CD28 antibody, improves psoriasis in the SCID mouse-psoriasis xenograft model. Journal of Investigative Dermatology, 128(8), 1969-1976. https://doi.org/10.1038/jid.2008.38
31. Lakshmipathi, T., et al. (1977). Photochemotherapy in the treatment of psoriasis. British Journal of Dermatology, 96(6), 587-594.https://doi.org/10.1111/j.1365-2133.1977.tb05201.x
32. Feldman, S.R., et al. (2008). Psoriasis: improving adherence to topical therapy. Journal of the American Academy of Dermatology, 59(6), 1009-1016.https://doi.org/10.1016/j.jaad.2008.08.028
33. Lebwohl, M. (2005). A clinician's paradigm in the treatment of psoriasis. Journal of the American Academy of Dermatology, 53(1), S59-S69.https://doi.org/10.1016/j.jaad.2005.04.031
34. Levin, A.A., A.B. Gottlieb, and S. Au. (2014). A comparison of psoriasis drug failure rates and reasons for discontinuation in biologics vs conventional systemic therapies. Journal of drugs in dermatology: JDD, 13(7), 848-853.https://doi.org/10.1016/j.cgh.2011.03.020
35. Younossi, Z.M., et al. (2011). Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clinical Gastroenterology and Hepatology, 9(6), 524-530. e1.
36. Yimin, Z., G. Keqing, and W. Zeshu. (Year). Study on evaluation model of cross-border e-commerce talent based on AHP-PSO. Paper presented at the 2016 2nd International Conference on Information Management (ICIM). Type retrieved fromDOI: 10.1109/INFOMAN.2016.7477525
37. Yi, Y., R. Nataraajan, and T. Gong. (2011). Customer participation and citizenship behavioral influences on employee performance, satisfaction, commitment, and turnover

intention. Journal of Business Research, 64(1), 87-95.https://doi.org/10.1016/j.jbusres.2009.12.007
38. Xie, J. (Year). SWOT analysis of cross-border e-commerce development in China under the Background of Internet Plus. Paper presented at the 2017 International Conference on Economics, Finance and Statistics (ICEFS 2017). Type retrieved fromhttps://doi.org/10.2991/icefs-17.2017.20
39. Xiaoyun, F. (2015). Research on B2C Cross-border Logistics Distribution Mode in E-commerce. Journal of Pingxiang University, 1, 008.
40. Wong, J.K.W. and J. Zhou. (2015). Enhancing environmental sustainability over building life cycles through green BIM: A review. Automation in Construction, 57, 156-165.https://doi.org/10.1016/j.autcon.2015.06.003
41. Wirtén, E.H. (2011). A Diplomatic Salto Mortale: Translation Trouble in Berne, 1884-1886. Book History, 14(1), 88-109.
42. Whang, S.-W., et al. (2016). Contractor-led critical design management factors in high-rise building projects involving multinational design teams. Journal of Construction Engineering and Management, 143(5), 06016009.
43. Wesolowski, A., et al. (2015). Impact of human mobility on the emergence of dengue epidemics in Pakistan. Proceedings of the National Academy of Sciences, 112(38), 11887-11892.https://doi.org/10.1073/pnas.1504964112
44. Wani, K.A. and P. Moorthy. (2014). Indus Waters Treaty: An Emerging Flashpoint Between India and Pakistan. Pakistan Horizon, 41-59.https://doi.org/10.1166/jctn.2017.6417
45. Wang, Y.-K. (2017). Model for Evaluating the Logistics Service Quality of Cross-Border E-Commerce Enterprises with Intuitionistic Fuzzy Information. Journal of Computational and Theoretical Nanoscience, 14(2), 1136-1139.
46. Prossick, T.A. and D.V. Belsito. (2006). Alefacept in the treatment of recalcitrant palmoplantar and erythrodermic psoriasis. Cutis, 78(3), 178-180.
47. Brimhall, A.K., et al. (2008). Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. British Journal of Dermatology, 159(2), 274-285.https://doi.org/10.1111/j.1365-2133.2008.08673.x
48. Chaudhari, U., et al. (2001). Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. The Lancet, 357(9271), 1842-1847.https://doi.org/10.1016/S0140-6736(00)04954-0
49. Lawry, M. (2007). Biological therapy and nail psoriasis. Dermatologic therapy, 20(1), 60-67.https://doi.org/10.1111/j.1529-8019.2007.00112.x
50. Papp, K.A., et al. (2008). Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). The Lancet, 371(9625), 1675-1684.https://doi.org/10.1016/S0140-6736(08)60726-6
51. Kirby, B., et al. (2001). Successful treatment of severe recalcitrant psoriasis with combination infliximab and methotrexate. Clinical and experimental dermatology, 26(1), 27-29.https://doi.org/10.1046/j.1365-2230.2001.00753.x
52. Katugampola, R., V. Lewis, and A. Finlay. (2007). The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. British Journal of Dermatology, 156(5), 945-950.https://doi.org/10.1111/j.1365-2133.2007.07817.x
53. Gottlieb, A.B., et al. (2004). Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. Journal of the American Academy of Dermatology, 51(4), 534-542.https://doi.org/10.1016/j.jaad.2004.02.021
54. Liang, S.C., et al. (2006). Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. Journal of Experimental Medicine, 203(10), 2271-2279.https://doi.org/10.1016/j.jaad.2004.02.021
55. Warren, R., et al. (2008). Methotrexate for psoriasis in the era of biological therapy. Clinical and Experimental Dermatology: Clinical dermatology, 33(5), 551-554.
56. Wang, W. (2016). Analysis and Evaluation of Chinese Cross-Border Electricity Supplier Logistics. Open Journal of Business and Management, 4(3), 500-504.
57. Au, S., et al. (2013). Comparison of the efficacy of biologics versus conventional systemic therapies in the treatment of psoriasis at a comprehensive psoriasis care center. Journal of drugs in dermatology: JDD, 12(8), 861-866.
58. Devaux, S., et al. (2012). Adherence to topical treatment in psoriasis: a systematic literature review. Journal of the European Academy of Dermatology and Venereology, 26, 61-67.

59. Armstrong, A.W., et al. (2013). Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA dermatology, 149(10), 1180-1185.
60. Augustin, M., et al. (2011). Adherence in the treatment of psoriasis: a systematic review. Dermatology, 222(4), 363-374.https://doi.org/10.1016/j.jaad.2010.11.055
61. Menter, A., et al. (2011). Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. Journal of the American Academy of Dermatology, 65(1), 137-174.