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Review Article

EVALUATION OF METHOTREXATE EFFICIENCY IN COMPARISON TO ALTERNATIVE DRUGS FOR THE TREATMENT OF PSORIASIS IN THE UK ADULT POPULATION: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Psoriasis is a skin condition that affects elbows, knees, back and scalp. It forms thick red patches of dead skin in the affected area where the dermis becomes red and swollen.

Objectives: To compare and evaluate the uses of methotrexate and other drugs; and their efficiency on psoriasis using various clinical studies.

Method: Research for randomised controlled trials has been done. These describe treatment investigations used in clinical practice. A systematic literature search has identified 10 clinical trials.

Results: The first clinical study observed that infliximab was more successful than methotrexate in treatment of moderate to severe psoriasis. Infliximab was administered intravenously and methotrexate orally. The treatment with infliximab started with 653 patients, from which 541 have completed the treatment successfully. The progression of disease during the treatment 0 and only 9 patients switched treatment. The total amount of patients who started the methotrexate treatment was 215 from which 127 have successfully completed it. The progression of disease was 2 and 63 patients switched treatment. In the last study it was also found out that a treatment with infliximab and methotrexate together is more effective than administering them on their own. The adverse event was 0, treatment fail 1 and a total of 17 subjects of 20 were successfully treated. It has been observed that methotrexate was significantly less effective than ustekinumab, etanercept and ABT-874. An alternative

treatment with efalizumab has been found to treat subjects who have a contraindication to methotrexate.

Conclusion: This systematic review shows that treatment with methotrexate only is less effective than combined with other drugs. A good alternative is to combine it with infliximab or to administrate other medicines found to be more successful in treating adult patients with severe psoriasis.

Keywords: Methotrexate; Infliximab; Psoriasis; Ustekinumab; Etarnecept

INTRODUCTION

Psoriasis affects around 2% of UK population and affects both men and women to the same degree. This condition shows a higher prevalence in adults below 35 years of age (NHS 2015) and results from an increased production of skin cells (Menter and Stoff, 2010). In healthy individuals, the process of synthesising and replacing the cells takes about four weeks, however in psoriasis it only takes up to 7 days. Psoriasis is an inherited autoimmune disease and as transmission is genetic, psoriasis is not contagious (Nicholson, 2016). Psoriasis is most often diagnosed by examination of affected regions and the appearance of the skin. In some cases a biopsy can be done where a sample is taken from the skin to be examined in a laboratory. After this procedure, an adequate treatment is administered. Although there has not been any cure developed for psoriasis, there are various drugs that can reduce the symptoms and appearance of the skin (Philipp *et al*., 2015). The BNF (British National Formulary) recommends drugs such as acitretin, cyclosporine and methotrexate (National Institute for Health and Care Excellence 2017). Of these, Methotrexate is widely used and carries with it significant drawbacks.

Methotrexate is a folic acid antagonist which is used to treat different medical conditions for example psoriasis or rheumatoid arthritis. Methotrexate inhibits the dehydrofolaxte reductase enzyme (DHFR) which is responsible for DNA synthesis and IL-6 and IL-1β (Flynn and Provost 2001). Additionally, adenosine release increases which carries with it anti-inflammatory effects. Methotrexate was first discovered in 1950 but started to be used to improve psoriasis in 1970 (Bieber and Nestle, 2015).

In this review the medical management of psoriasis has been examined to evaluate conventional treatment of psoriasis with methotrexate in comparison with more recent and alternative approaches.

SUMMARY OF AIMS AND OBJECTIVES

The primary aim of this research was to produce a systematic review on psoriasis and the drugs administered to reduce its signs and symptoms. The objectives were:

1. Systematically examine open access publications which report on the treatment of psoriasis with methotrexate and comparisons with other drugs.
2. Implement the PRISMA flowchart and checklist to filter and extract only the relevant clinical trials.
3. Draw attention to psoriasis treatment with methotrexate, its advantages, disadvantages, alternatives and its impact on the quality of life.
4. If possible perform meta-analysis can be done regarding to the results extracted from each randomised clinical trial.

METHODS

The PRISMA flow diagram has been used to select the studies. All of these stages were documented clearly in the PRISMA flow diagram Figure 1. PRISMA has set a checklist which highlights the minimum 27 points which are needed in a systematic review or meta-analysis. This study selection method is for screening, determining eligibility, inclusion in the systematic review. This minimises data dredging and reduces bias because the diagram is systematic reproducible and also explicit.

INFORMATION SOURCES AND SEARCH

The data bases used to search were: EU Clinical Trials Register, PubMed, Google Scholar and Scopus. The key words for the search box was 'methotrexate OR psoriasis and methotrexate' to obtain the 757 results. Then search filters were included to reject the trials which are not needed to analyse. Trials with patients who suffer from psoriasis were selected. All the trials observed had results but the last two were repeats therefore, they have not been

discussed and analysed to avoid bias. A total of 10 clinical trials were included out of 12. Only randomized controlled trials were included comparing treatment strategies for the management of moderate to severe psoriasis. All of the reports were published in English. Only adult participants with psoriasis were considered. Trials are comparing the beneficial effects of methotrexate and other drugs on moderate to severe psoriasis.
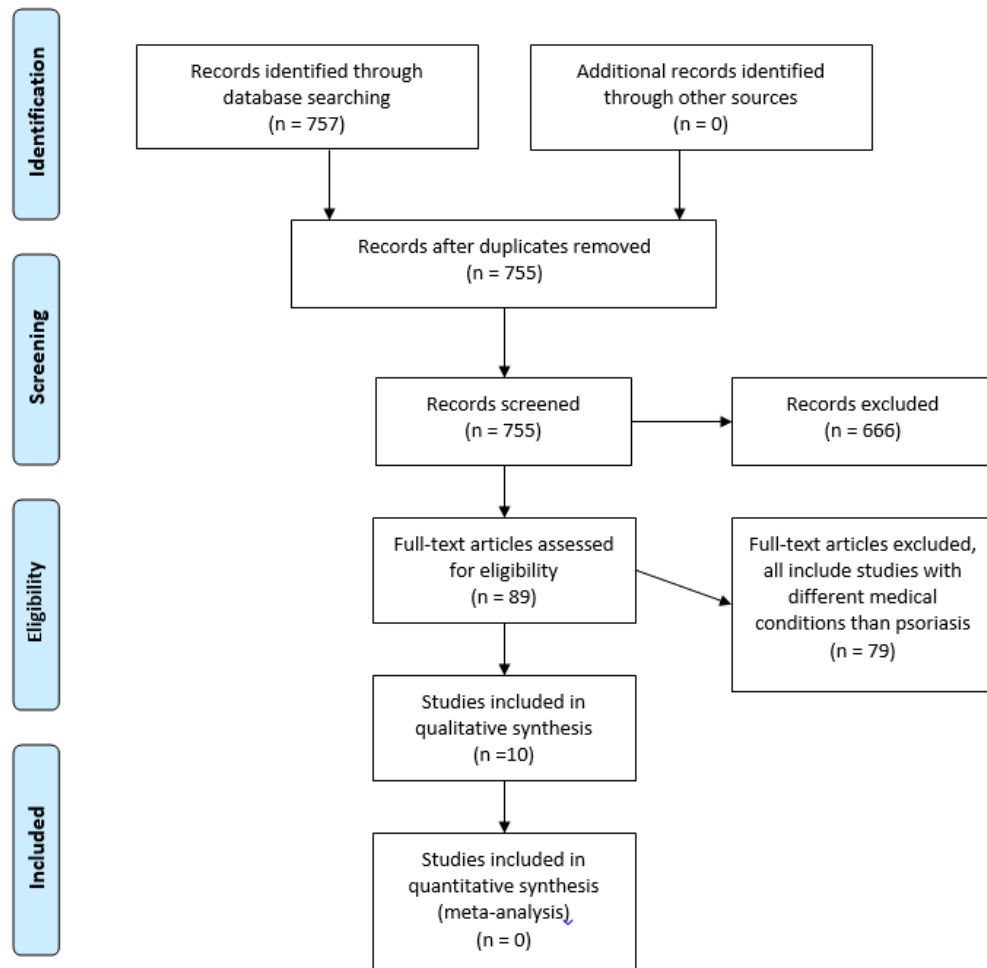

Figure 1: PRISMA flow chart.

The data collection method was the pilot method. After a wide range of clinical trial papers were found, data from the sample papers were extracted and appraised for validity and quality followed by a sample synthesis.

Information was extracted from each trial on: characteristics of trial subjects such as age, stage and severity of the disease, type and dosage of the drug and duration of the trial.

ELIGIBILITY CRITERIA

A total of 10 trials were identified for inclusion in the review. The searches of all 5 databases provided a total of 755 citations after duplicates were removed. A total of 344 trials were rejected because they were not completed. Only trials with validated results were chosen, therefore 483 were excluded out of the total because the trials did not contain any results. This review is only based on studies from adults, therefore 61 samples were also removed. Both male and females have been considered therefore 21 trials have been excluded because 19 were only focused on females, and 3 only on males. Other 2 studies were discarded because they were repeats. Out of the total, 16 studies were focused on different medical condition and therefore have been discarded. Ten studies meet the inclusion criteria and were included in the review.

RISK OF BIAS

Bias is the deviation from the truth which always influences the results of an experiment and analysis .The risk of bias identifies the risk of a systematic error in the results. The heterogeneity between all the trials` results of a systematic review can be accredited to bias of different degrees. The aim of a systematic review is to reduce the risk of bias as much as possible to obtain the most valid conclusion. It ensures that all the clinical trials are thoroughly analysed eliminating the risk of bias from study selection. The eligibility criteria has been used to identify the right articles for the systematic review. Only original clinical trials have been used therefore the original methods were given by the authors in comparison with a review article where data may be interpreted by another person, increasing the risk of bias. Secondly, the JADAD scale was used which assesses the trials and risk of bias in this systematic review (Jadad *et al.,* 1996). This scale represents 5 questions and by answering every question 1 point is achieved if the answer is positive. If 4 or 5 points are achieved then the risk of bias is very low. If only 3 points are achieved then the risk of bias is on the medium level in comparison with 1 or 2 points at which the risk of bias is at a high level.

Three items are assessed using the JADAD scale: withdrawals and dropouts, binding and randomisation.

Data screening for meta-analysis Meta-analysis is a statistical procedure of combining data or different studies in order to answer a research question. The data has been screened in order to determine if a meta-analysis can be done. From each trial the results were extracted to observe if they have been focused on the same data points and stages of the trial so they can be compared and analysed. For example data was screened to see how many of the clinical trials focused on the PASI75 and what results they obtained.

Results

The majority of the randomized control clinical trials took 3 years to be completed and published. The trial that took the least time is the treatment with adalimumab which took 1 year to finalise completely.

The first clinical trial was a phase 3 trial which was first received on September 2005 and completed on June 2008.The trial measured the effect of infliximab versus methotrexate in treatment of moderate to severe psoriasis over 26 weeks (EU Clinical Trials Register 2008). The trial took 3 years to be completed. The interventions received in the first trial were 2.5mg tablets once a week on subjects treated with methotrexate and 5mg/kg of infliximab administered intravenously over a period of 2 hours. The total of subjects enrolled for treatment was 868 from where 653 were analysed on infliximab and 215 on methotrexate. The primary outcome measures for the trial was the PASI75 response at week 16 (78% in response to infliximab and 42% after methotrexate was administered). Psoriasis Area and Severity Index (PASI) is the measurement of severity of psoriasis. It is often presented as percentage response rate for example PASI50, PASI75, PASI90 or PASI100. PASI75 represents the percentage of subjects who achieved 75% reduction in PASI score from baseline. PASI100 indicates subjects who obtained a complete resolution of disease (Healthline, 2016). The secondary outcomes measures were to observe the PASI75 response at week 26 (77% and 31% after the treatment with infliximab and methotrexate respectively) and to find out the proportion of participants who achieved a Physician`s Global Assessment (PGA) score of 'Cleared' or 'Minimal' at week 16 (76% and 38%) and 26 (73% and 28%).

PGA also assesses the severity of psoriasis PGA scale ranges from 0 describing no disease present, to 5 which indicate severe psoriasis. 'Cleared' or 'Minimal' include subjects who were scored 0 or 1 indicating no psoriasis or mild psoriasis. Moderate psoriasis is indicated by a PGA score of 2 or 3 and therefore severe psoriasis has a PGA score of 4 or 5 (Healthline, 2016).

The second trial (EU Clinical Trials Register 2007) was describing the effect of efalizumab on patients who have a contraindication to methotrexate. It was a 3b/4 phase trial over 24 weeks of treatment. The duration of the intervention was 3 years but results were only obtained in the first year. The total number of subjects taken part in this experiment was 1266. Efalizumab was administered subcutaneously at 1.0 mg/kg once a week with a control dose of 0.7mg/kg. The primary study objective was to establish control of psoriasis with efalizumab treatment and secondly, to evaluate the management of the events in the disease: rebound and exacerbation during the treatment or after. PGA was measured at week 12 (n=1255) was 68% 'Good or better' and PASI respectively meaning that there is a decreased progression of the disease and symptoms respectively, leading to a lower severity of psoriasis such as mild psoriasis At baseline, the median PASI was 19.55 because 51.3% of patients had the PASI baseline lower than 20. The efalizumab treatment on patients who have a contraindication to methotrexate resulted with 79.5 % improvement on the continuous treatment (CT) period and had a PGA of 'Good' or better at the end of treatment. During the retreatment (RT) period there was 55 % improvement and the PGA rating was 'Good' but musculoskeletal disorders appeared during RT period.

The third trial (EU Clinical Trials Register 2011) was a phase 3b/4 which took 2 years to complete. The treatment with ustekinumab after methotrexate was assessed over 52 weeks. There were 1090 subjects which took part in the randomised clinical trial. Ustekinumab (0.5ml) was administered subcutaneously. The primary objective of this study was to evaluate and compare previous treatment with methotrexate to immediate initiation of ustekinumab. There were also secondary outcomes: to evaluate safety and efficacy of the treatment over 52 weeks; to evaluate effects of increasing dose of drug in week 28 and week 40 from 45 mg to 90mg for patients who did not receive PASI75 and PGA responses at weeks 28 and 40. Their evaluation showed further improvements because of the increased ustekinumab dose.

The fourth clinical trial (EU Clinical Trials Register Apr 2013) described the effect on studies in whom psoriasis has reported to initial treatment with etanercept of two different strategies in managing a response. It is a phase 4 trial in which the drug treatment lasted 52 weeks. The trial has been completed in 3 years. The first dose administered to subjects was 25 mg of drug once a week. They also had the option to increase their dosage to 50 mg/ week depending on the effect of the drug on the disease. The drug was injectable. The primary outcomes were to observe the effect of the drug on the disease. There were also secondary outcomes: to compare the efficacy of treatment on the quality of life; to explore the satisfaction degree of treatment. As a result, it has been showed that the quality of life improved after taking the medication.

A comparison of tofacitinib and placebo was also observed after 56 weeks treatment with the drug (EU Clinical Trials Register June 2013). It was a phase 3 trial which was completed in 3 years. The total number of subjects that took part in this study was 209. The dosage of drug administered was 5mg twice daily (BID) and respectively 10 mg. BID is the abbreviation for the Latin words "bis in die "which mean "twice a day". The primary outcomes were to compare the efficacy and response of the two doses and also results with the placebo during the 4th and 16th week. The secondary outcomes were the evaluation and efficacy measurement of both doses during the 56 weeks of treatment. Both doses of tofacitinib were tolerated well during period A therefore there were a few safety events in B and C period. Cardiovascular events were reported for 3 patients: 2 subjects suffered fatal myocardial infraction and artery bypass grafting in period A taking the 5 mg dose. One subject suffered a peripheral vascular disease and percutaneous transluminal coronary angioplasty in period B taking the 10 mg dose of tofacitinib. There was 1 death reported in the 5mg dose BID during period A. The subject suffered a fatal myocardial infraction. During the study 8 patients had herpes zoster out of which 7 were administered the higher dose of drug (10 mg BID). Of those who lost adequate response on placebo during the withdrawal period 31.6% and 41.4% on 10 mg BID regained the PGA response and PASI75 after 16 weeks of retreatment with tofacinitib.

The sixth study (EU Clinical Trials Register Nov 2009) was a 52 week phase 3 study comparing the effects or ABT-874 and methotrexate on adults with psoriasis taking 18

months to be completed. Treatment A was administering ABT-874 subcutaneously in 200 mg at baseline (week 0) and week 4. Then 100 mg was administered from week 12 to week 48. Treatment B with methotrexate contained 5 mg to 25 mg capsules weekly dosing at week 0 to week 51. The primary and secondary outcomes are based on the effects of the treatment at week 12 to week 51. The results of this study over 52 weeks demonstrated the safety and efficacy of the drug to reduce the symptoms of psoriasis. Treatment with ABT-874 resulted in a more rapid clinical response than methotrexate. The safety profile of ABT-874 was similar to methotrexate in this study. There were no safety concerns.

Treatment with analimumab has been also monitored for 16 weeks (EU Clinical Trials Register Oct 2008). It was a phase 3 trial completed over 12 months. There was a total of 730 subjects were analysed for efficacy and safety. The drug 40 mg/0.8 ml was administered subcutaneously. Primary and secondary outcomes were focused on the evaluation of the progression of the disease using the drug in combination with topical psoriasis treatment, calcipotriol/betamethasone, versus analimuman with matching vehicle. Analibumam was safe and tolerated well among subjects in this study. It demonstrated substantial efficacy when PASI, PGA and Dermatology Life Quality Index (DLQI) responses were monitored over 16 weeks. DLQI is a questionnaire used to assess the effect of skin disease on affected people. PASI75 of analibumam+ C/B was 64.8% while analibumam+vehicle measured 70.9%. The DLQI mean percent was 67.2% (analibumam and C/B) versus 71.46% (analibumam and vehicle). PGA clear and minimal response rates were 56.6 % and 64.6% respectively. PGA clear response measured a percentage of 18% versus 29.9%.

The next trial had compared tofacitinib to etanercept and both to placebo (EU Clinical Trials Register Jan 2013). The results were taken in the first 12 weeks and the trial was completed in 12 months. The primary objectives were to compare the efficacy (PASI75 and PGA response) of tofacinitib 5 mg and 10 mg twice daily versus etanercept 50 mg twice daily after 12 weeks. At week 12, the PASI75 and PGA responses were higher in the subjects with tofacinatib 10 mg BID than etanercept 50 mg. All treatment groups had a higher response rate compared to the placebo group. The PGA measured 'clear' or 'almost clear' at the start of week 8 for tofacitinib 10 mg and etanercept 50 mg. In the 5 mg tofacitinib group PGA was measured after 12 weeks.

A study comparing efalizumab and placebo had been also observed (EU Clinical Trials Register Mar 2009). The treatment lasted 24 weeks in which results were obtained and the trial completion took place after 15 months from the start of the treatment. It was determined that efalizumab is superior to placebo. During the efalizumab double blind period 1.96% of subjects from a total of 51 was at risk or affected.

The last trial compared the effects of treatment with infliximab and methotrexate and infliximab alone (EU Clinical Trials Register Apr 2011). The trial took 2 years to complete and the results were only taken in the first 28 weeks. As primary outcomes, PASI75 was assessed at week 28. There were a few secondary outcomes to be determined: PASI50, PASI90, PASI100, DLQI and EQ-5D (Euro-Qol 5 Dimension). The EQ-5D is a descriptive system with the following dimensions: depression, pain, self-care, mobility and usual activities. Subjects are asked to choose one of the above to describe their health state.

Table 1: Measured values of PASI75 at week 28.

	IFX (infliximab)	IFX (infliximab)+ MTX(methotrexate)
SUBJECTS	17	19
PASI75 AT WEEK 28	9	11

There is no statistical analysis provided for PASI50, PASI90, PASI100, DLQI and EQ-5D at week 28 because there were no participants analysed.

There were 5.56% of subjects at risk during the treatment with IFX in comparison with the INF+MTX treatment where the risk was recorded to be 0.00%.

The score achieved for the systematic review after using the Jadad scale was 4 in the majority of the trials which identifies that there is a low risk of bias introduced. All of the trials were randomised controlled trials. The majority of the trials were double blind, including a placebo but there were no mentions about withdrawals or dropouts.

DISCUSSION

Most of the times it`s really hard for doctors to choose which medicine to prescribe to patients for a particular disease if there is a numerous range of drugs which can treat that disease. This systematic review compared and described the effect of different treatments that can be used to treat psoriasis. By administering the right drug treatment and dosage can decrease the risk of liver damage and other side effects to patients. The quality of life will also improve quicker because there won`t be any treatment change needed. The 10 different trials follow the same eligibility criteria comparing two different drugs or a drug with a placebo and then the results were analysed to determine which drug had a better effect and why. Methotrexate and its effect on psoriasis are well documented but following examination of the literature, it was found that other drugs such as infliximab had better effects on psoriasis than methotrexate when compared in the first trial assessed (Weinberg 2008). Furthermore, a combination of methotrexate and infliximab gave better results than the treatment of each drug on its own. A treatment change from methotrexate to ustekinumab for patients who did not show any improvements was assessed. This concluded that methotrexate did not have a positive effect in all the subjects. To decrease other complications in subjects, only the ustekinumab treatment could have been administered, without the methotrexate in the first place. ABT-874 showed to have more effect than methotrexate as well. Various other clinical trials were also double blind and as a result, their treatment showed a critical improvement in condition e.g. analimumab, tofacitinib and efalizumab. Although methotrexate was the first drug to be used against psoriasis, it is clearly shown that today`s medicine evolves and other drugs have been discovered to improve even further the symptoms and quality of life of patients. Weinberg has agreed with the results and conclusions of this systematic review because he states that. In January 2003 FDA approved several medications for psoriasis such as etanercept, efalizumab and infliximab (Weinberg, 2008).

In addition to psoriasis, methotrexate can also be used to treat rheumatoid arthritis, cancers and also other autoimmune diseases such as Crohn`s disease and Lupus. It has different mechanisms of reaction upon all the different disorders according to Castillo and Moyano (Castillo and Moyano, 2012). As well as inhibiting DHFR, methotrexate also inhibits the

action of the enzymes involved in purine metabolism therefore, as described in the introduction, adenosine production increases and therefore inflammation decreases (Ohno *et al.,* 2016). In the autoimmune diseases the cytokine and T cells production increases because the immune system attacks healthy tissues in the body (Brauna and Rau, 2009). Methotrexate also lowers cytokine production but the mechanism of action is unknown yet. Another mechanism is based on the accumulation of polyamides in the synovium of rheumatoid arthritis patients. The metabolism of polyamides releases toxic oxygen products which then lower the function of T cells. Antigen stimulated T cell proliferation is also reduced by methotrexate but its mechanism unknown (Brauna and Rau, 2009).

Duffin and Krueger 2009 stated that genetic variants play an important role in psoriasis. Current research has observed that HLA-Cw6 on chromosome 6 is the risk factor of the major psoriasis susceptibility locus PSORS1. This increases the risk of developing psoriasis. Other recent studies have discovered gene encoding cytokines which are linked to the onset of psoriasis. Polymorphisms with IL-13 (Th2 cytokine) increase the risk of psoriasis. Genes encoding the IL-12 p40 subunit, IL12B and IL23R have been replicated and results showed that they increase the risk of developing Crohn`s disease. Another study has been performed on Chinese subjects and results demonstrated that polymorphisms encoding the IL-15 were identified that associate with psoriasis. Psoriasis has always been considered as a genetic disorder supported by evidence of the disease spreading within members of the same family. In the results section, there has been observed that ustekinumab improved the quality of life of psoriatic patients. Ustekinumab is a biologic drug which targets and inhibits IL-12 and IL-23 therefore decreasing the symptoms of the disease and preventing it from spreading.

An evidence based dermatological study was performed by Kirsner el al., 2009 which concluded that subjects with psoriasis are at risk of developing cardiovascular diseases. It was found out that patients who suffer of psoriasis experience a high prevalence of peripheral arterial disease, ischemic heart disease and also cerebrovascular disease. Therefore, psoriasis is described as an independent factor of mortality. The study has discovered a much higher percentage of mortality in subjects who suffer from psoriasis (19.6%) than healthy subjects (9.9%). Psoriasis is an autoimmune disease and therefore it causes the immune system to react to a threat. This reaction of the immune system causes inflammation. In psoriasis, this

inflammation takes form in red patches of skin on the body. Blood vessels may also be inflamed. This can contribute to atherosclerosis. Atherosclerosis is a build-up of plaque inside the arteries, on their walls, which then prevent the blood from passing through towards the heart, therefore; increasing the risk of heart disease. People with psoriasis have a risk of suffering a heart attack almost three times more than people without psoriasis. Some treatment of psoriasis includes drugs which can lead to irregular cholesterol levels. This can contribute to atherosclerosis increasing the risk of heart attack even more (Watson and Roth, 2016).

Armstrong *et al.* 2017 proposed that after tofacitinib treatment of psoriasis, there were small increase of LDL and HDL cholesterol. Paraoxonase 1 activity (protein associated with HDL antioxidant capacity and HDL binding) increased. Systematic inflammation and serum amyloid A which lowers the anti-atherogenic potential of HLD decreased. The blood pressure and glycated haemoglobin levels did not change, but C-reactive protein levels decreased. C-reactive protein is a substance secreated by the liver which increases the inflammation throughout the body. While the treatment with tofacitinib resulted in small increase in cholesterol levels, the total ratio of HDL cholesterol did not change. Therefore there are no unfavourable changes in some CV risk factors (Ahlehoff *et al.,* 2016).

In this systematic review different drugs were observed to cure psoriasis. Further clinical research might be done in future in early, medium and late stage of psoriasis to find out which drug is best at which stage. This will improve medical approach and therefore the appropriate drug will be administered to patients depending in which stage is the disease. This might increase the improvement of patients` health in a smaller time interval. The reaction of some of the drugs might be able to improve psoriasis at a later stage while some of the drugs might not be powerful enough to overcome the symptoms therefore they may be administered at an early stage. Also further research might also relevant in the discovery of a drug which can totally cure psoriasis.

LIMITATIONS

There are some limitations for this review which should be recognized and accepted. A significant conclusion could not be met because a meta- analysis was not done. This is due to

the non-comparable data from all the clinical trials. Other limitation was that the clinical trials examined were only in the English language. Also, only free full text articles could be accessed meaning that other relevant literature might have been unused because of this restriction.

CONCLUSION

In conclusion, this systematic review has been able to underline the benefits of medicine on psoriasis and also describing how they are able to decrease the progression of the disease. The majority of the drugs suggested are relatively new discovered e.g. ustekinumab and tofacitinib but also old drugs e.g. methotrexate. A comparison between the old and new drugs was observed which then gave a deep comparison of their effects on psoriasis and improvement of symptoms. Overall, drug development seems to be present in the improvement of psoriasis, but the question is now weather there will be a way of curing it.

REFERENCES

1. Ahlehoff, O; Egeberg, A; Hansen, PR; Qureshi, AA; Robertson, D; Strober, BE; Tan, H; Wolk, R and Wu, JJ (2016) "Effects of tofacitinib o cardiovascular risk factors and cardiovascular outcomes based on phase III and long-term extension data in patients with plaque psoriasis." *J Am Acad Dermatol* 75: 897-905.

2. Armstrong, EJ; Hensen, PR; Kaur, M; Lan, S; Tallman, AM; Tatulych, S and Wold, R (2017) "Effect of tofacitinib on lipid levels and lipid-related parameters in patients with moderate to severe psoriasis." *J Clinical Lipidology* 11: 1243-1256.

3. Bieber, T and Nestle, F (2015) "Personalized Treatment Options in Dermatology." *Germany: Springer.*

4. Brauna, J and Rau, R (2009) "Mechanisms of action of methotrexate." *An update on Methotrexate* 21: 216-223.

5. Castillo, VS and Moyano, LA (2012) "Methotrexate: Pharmacology, Clinical Uses and Adverse Effects." New York: *Nova Science Publishers.*

6. Duffin, KC and Krueger, GC (2009) "Genetic Variations in Cytokines and Cytokine Receptors Associated with Psoriasis Found by Genome-Wide Association". *J Investigative Dermatol* 129: 827-833.

7. EU Clinical Trials Register (2007) "A multicentre, open label Phase IIIb/IV study of subcutaneously administered efalizumab in the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including ciclosporine, methotrexate and PUVA."

8. EU Clinical Trials Register (2008) "A Multi-center, Randomized, Vehicle-Controlled Study to Assess the Efficacy and Safety of Adalimumab in Combination with Topical Treatment (Calcipotriol/Betamethasone) in Subjects with Moderate to Severe Psoriasis and Insufficient Response to Classic Systemic Treatment (BELIEVE)."

9. EU Clinical Trials Register (2008) "An Open-Label, Randomized Efficacy and Safety Study of Infliximab Versus Methotrexate in the Treatment of Moderate to Severe Psoriasis."

10. EU Clinical Trials Register (2009) "A Phase 3, Multicenter, Randomized, Double-blind Study Comparing the Safety and Efficacy of ABT-874 to Methotrexate in Subjects with Moderate to Severe Chronic Plaque Psoriasis."

11. EU Clinical Trials Register (2009) "A Phase IV multicentre, randomised, double-blind, placebo controlled, trial to evaluate the safety and efficacy of Raptiva ® in the treatment of subjects with moderate to severe plaque psoriasis involving hands and/or feet, with or without pustules."

12. EU Clinical Trials Register (2011) "A Study of Dose Optimization of Infliximab in the Treatment of Moderate to Severe Plaque Psoriasis."

13. EU Clinical Trials Register (2011) "An Exploratory Trial To Assess Naturalistic Safety And Efficacy Outcomes In Patients Transitioned To Ustekinumab From Previous Methotrexate Therapy (Transit)."

14. EU Clinical Trials Register (2013) "A Phase 3, Multi Site, Randomized, Double Blind, Placebo Controlled, Parallel Group Study Of The Efficacy And Safety Of 2 Oral Doses Of Cp-690,550 And 1 Subcutaneous Dose Of Etanercept In Subjects With Moderate To Severe Chronic Plaque Psoriasis."

15. EU Clinical Trials Register (2013) "A Phase 3, Multi-Site, Randomized, Mixed-Blind, Parallel-Group Treatment Withdrawal And Re-Treatment Study Of The

Efficacy And Safety Of 2 Oral Doses Of Cp-690,550 In Subjects With Moderate To Severe Chronic Plaque Psoriasis."

16. EU Clinical Trials Register (2013) "Randomized Open-label Study Comparing 2 Different Strategies For Management of Subjects With Plaque Psoriasis Who Have Responded to Etanercept Treatment."

17. Flynn, JA and Provost, TT (2001) "Cutaneous Medicine: Cutaneous Manifestation of Systemic Disease." London: BC Decker Inc. London.

18. Healthline (2016) "Understanding Psoriasis."

19. Jadad, AR; Carroll, D; Gavaghan, DJ; Jenkinson, C; McQuay, HJ and Moore, RA (1996) "Assessing the quality of reports of randomized clinical trials: is blinding necessary?" *Control Clin Trials* 17: 1-12.

20. Kirsner, RS, Kravetz, JD and Prodanovich, S (2009) "Association of Psoriasis With Coronary Artery, Cerebrovascular, and Peripheral Vascular Diseases and Mortality". *Arch Dermatol* 145: 700-703.

21. Menter, A and Stoff, B (2010) "Psoriasis." *London: Manson Publishing Ltd.*

22. National Institute of Health and Care Excellence (2017) "Psoriasis."

23. NHS (2015) "Psoriasis."

24. Nicholson, LB (2016) "The immune system." *Essays in Biochem* 60: 275-301.

25. Ohno, S; Orefice, F; Pavesio, C; Rao, NA and Zierhut, M (2016) "Intraocular Inflammation." London: *Springer.*

26. Philipp, S; Sabat, R and Sterry, W (2015) "Psoriasis: Diagnosis and Management." *John Wiley & Sons Ltd.: Oxford*.

27. Watson, K and Roth, E (2016) "The Heart-Psoriasis Connection: What you need to know."

28. Weinberg, JM (2008) "Treatment of Psoriasis." Boston: Birkhauser Verlag AG, Basel.

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