A Pharmacovigilance Study on FDA Approved Interleukin Inhibitor-Associated Alopecia in the Treatment of Psoriasis

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled " A Pharmacovigilance Study on FDA Approved Interleukin Inhibitor-Associated Alopecia in the Treatment of Psoriasis" submitted by Nahidul Islam – 19146034 of Spring 19 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on February 2023.

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Dedication

Dedicated to my Faculty members, Family, Friends and Relatives

Ethics Statement

The project was carried out using data collected from the FDA Adverse Event Reporting System (FAERS) and does not involve any participants from clinical trials, either human or animal. Furthermore, neither humans nor animals are harmed by the project.

Abstract

FDA has approved about 12 biologics for treating psoriasis. Among them, TNF-α inhibitors have a history of causing alopecia while used for treatment. In our study, we tried to find out the relation between alopecia and the FDA-approved biologics that are interleukin inhibitors while treating psoriasis. In our study, we include data from FDA Adverse Event Reporting System (FAERS) to find out Reporting Odds Ratio and Confidence Interval (CI). For interleukin inhibitors Ustekinumab, Guselkumab, Brodalumab, Ixekizumab and Secukinumab, the lower bound of CI were less than 1. We did not find any value for Tildrakizumab and Risankizumab. We did not find any signal for adverse event Alopecia. There are several cases available that says that, IL-17A causes alopecia when given to patients. More investigation is required to find out connection between them for the safety and find better alteration of these drugs if needed.

Keywords: Psoriasis; Biologics; FAERS; Interleukin inhibitors; Alopecia; Pharmacovigilance.

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PV – Pharmacovigilance

AA- Alopecia Areata

PsA – Psoriatic Arthritis

Chapter 1

Introduction

1.1 Psoriasis

Psoriasis is a common chronic skin inflammation that is present worldwide. Defective keratinocyte differentiation and high epidermal development are known to be the causes of psoriasis (Kimmel & Lebwohl, 2018). By 2021, there will be more than 7.5 million psoriasis patients in the United States, and psoriasis affects nearly 2–3% of the global population. To help raise awareness of psoriasis, the 29th of October is declared "World Psoriasis Day" every year (Psoriasis: Causes, Triggers and Treatments, 2021). According to the MAPP survey, the prevalence of psoriasis is 1.4–3.3% in Spain and 1.9% in Canada. In Bangladesh, psoriasis is not a very common disease. According to a survey, it is estimated that, around 0.7% of the population of Bangladesh suffers from psoriasis (Bhuiyan et al., 2020). Among them, 81% have plaque psoriasis. The common symptoms present among them are itching, burning, and joint pain. The average age of people suffering from psoriasis was 37 +/- 2.7. In addition, about 8.4% have an association with their family (Bhuiyan et al., 2020). Psoriasis is a condition that affects people globally, although the prevalence varies by region. Both males and females can develop this skin condition at any age, but psoriasis is most common in people between the ages of 20 to 30 and 50 to 60. Any first-degree relative of psoriatic patients has a 30% probability of developing the disease at some point in their lifetime (Kimmel & Lebwohl, 2018).

In psoriasis, three types of conditions affect hair loss and they are, a) alopecia occurring only to limited lesion of the skin, b) alopecia occurring due to telogen effluvium; and lastly, c) scarring alopecia. Among them, (a) is the most common cause of hair loss in psoriasis. Moreover, reduction of hair density, reduction of finer hair as well as increase in dystrophic bulb is seen among patient with psoriasis. It was found that, removal of hair was easy for

patients who have psoriasis on their scalps. The removed hair had a conglomeration of scales on it. Loss of hair happened on an average after six weeks from the occurrence of psoriasis. However, studies show that, when patients started local therapy, about 28% got alopecia. In another study, which constituted 47 patients with scalp psoriasis, it was shown that, about 47% of them had more hair loss (about 480 hair loss per day) than average people. Psoriasis causes a reduction in the number of anagen hairs and a higher amount of telogen hair. This causes a significant effect on the growth of hair during psoriasis. Pustular psoriasis on the scalp will cause temporary hair loss along with regrowth of hair after a certain time (George et al., 2015). There are several types of alopecia available. For example, chemotherapy induced alopecia, androgenic alopecia, alopecia areata (AA), anagen and telogen effluvium, and so on (Rambwawasvika, 2021). Patients who have psoriasis have an odds ratio (OR) of 2.5 for developing alopecia (George et al., 2015). Additionally, topical psoriasis treatment can cause hair loss by causing telogen hair to fall out. Alopecia Areata (AA) is a form of autoimmune disorder that targets the hair follicles with T cells. The use of chemotherapeutic drugs throughout various treatments results in chemotherapy-induced alopecia (CIA). These drugs attack rapidly expanding cells like keratinocytes that are in the anagen phase and cause alopecia. However, hairs begin to grow more quickly after stopping chemotherapy treatments because many newer hair follicles are being produced. Another type is androgenic alopecia, which is more common in men than women due to the excess release of testosterone. It causes baldness in men mostly and scalp hair thinning in women. Anagen and telogen effluvium is another type of alopecia. When hair starts to fall out in an anagen state due to any medication, it is known as anagen alopecia. In this type, the telogen phase (inactive phase) is longer and lasts until medication is discontinued. Telogen alopecia is a chronic condition that occurs to people who has thyroid or hormonal problem, stressful life and old aged people (Rambwawasvika, 2021).

Excessive proliferation and insufficient differentiation induce psoriasis, and inflammation caused by psoriasis, such as plaque psoriasis, might emerge (Gudjonsson & Elder, 2007). In this circumstance, the skin's epidermis will be attacked by the overly active immune system, which will cause it to shed in three to four days instead of the normal time, which takes around months. The skin will also experience increased blood flow in the cutaneous area and leukocyte infiltration of the papillary dermis (Psoriasis: Causes, Triggers and Treatments: National Psoriasis Foundation, 2022). The production of plaques in psoriasis produces itching and discomfort that can be excruciating. Once again, the skin condition psoriasis has a detrimental impact on the patient's physical health and lowers their quality of life. Today, it has been discovered that 75% of psoriasis patients experience comorbid conditions, meaning they may experience the onset of a different illness as a result of their psoriasis. Psoriatic arthritis is hypothesized to occur as a result of elevated cytokines in the body, which induce inflammation. Less than 10 percent to 40 percent of those with psoriasis are thought to develop psoriatic arthritis (Kimmel & Lebwohl, 2018). In addition, about one third of the psoriasis patients have the possibility of developing psoriatic arthritis (Ritchlin et al., 2017). PsA can occur in people aged 40–50 years, and it can occur on joints, skin, nails, etc. This can occur due to a genetic factor, an environmental factor, or an immunologic factor. PsA can develop in patients who are undergoing traumatic situations. Also, NK cells and CD8+ T cells are very much involved in the development of PsA due to activation in the synovium, where psoriasis occurs. Moreover, by using drugs, or other therapy for immunomodulation might be one of the causes of developing PsA. A study found that, patients who had psoriatic arthritis had an elevation in the amount of type 3 lymphocytes as well as Th17 cells, which are responsible for producing the proinflammatory substances Il-17A and IL-22 (Gladman, 2008). In another study, when PsA patients were given TNF-α inhibitors, 23 percent people had chance of diminishing PsA. But, when the patients stopped taking the drugs, PsA recurred (Ritchlin et al., 2017).

Psoriasis has a great negative impact not only on physical health but also on mental health. For a very long time, psoriasis has been called a psychosomatic disorder because psoriasis patients feel psychological distress or stress. In a recent study, it was found that more than 60% of patients with psoriasis reported having stress, and they felt it was a major factor in the cause of the disease. Another 2-year survey suggests that, they faced depression, self-consciousness, and increased worrying. There was also a relationship found between depression, suicidal thoughts, and psoriasis. More than 5% of the psoriasis patients feel depression and have suicidal thoughts. Moreover, there are also relation with sleeping difficulty with psoriasis. Another study tells us that, anxiety and worrying are found in 40% of psoriasis patients. However, stressful life has not had much effect on psoriasis (Griffiths & Richards, 2001).

Pharmacovigilance is the monitoring of drugs and vaccines after they have been marketed. Phase IV of any newly created drug or vaccine is when any side effects are examined by analyzing self-reported cases from the general public as well as an analysis of the sold product. PV entails the identification, comprehension, evaluation, and prevention of any negative effects associated with drugs or vaccinations. PV helps to make drugs safe and ensure rational use. But, self-reporting is one of the great sources of information for pharmacovigilance of drug or vaccine. Several countries are encouraging pharmaceutical companies to report adverse events to the regulatory authority. They are also motivating to keep a pharmacovigilance specialized person in the company. In addition, in some countries, they are also inspiring physicists and healthcare professionals to report adverse events (Meyboom et al., 1999). Managing signals, managing benefit-risk interactions, and managing cases are the three core functions of pharmacovigilance (Beninger, 2018).

1.2 FDA Approved Biologics for Psoriasis

There are currently 12 biologics on the market that have been approved by the FDA for psoriasis. They are adalimumab, tildrakizumab, infliximab, brodalumab, golimumab, risankizumab, ixekizumab, guselkumab, ustekinumab, certolizumab pegol, secukinumab, and etanercept. With the exception of golimumab, all of these medications have FDA approval for use in treating psoriasis. Again, there are other nine medications that can be used to treat psoriatic arthritis besides brodalumab, risankizumab, and tildrakizumab (PSORIASIS TREATMENT: BIOLOGICS, 2022).

TNF-α inhibitors such as Adalimumab, Certolizumab pegol, Etanercept, Golimumab, Inflimab and Interleukin inhibitors such as Secukinumab, Ixekizumab and Ustekinumab are used for PsA (Ritchlin et al., 2017).

1.3 Alopecia and Biologics

There is a clear connection visible between psoriasis and alopecia that was caused by the use of biologics. Alopecia, also known as hair loss, has been observed in patients with scalp psoriasis. Alopecia occurred due to scalp psoriasis and was cured by treatment.

1.4 Pharmacokinetics of the Biologics

The twelve approved biologics are given either subcutaneously or intravenously. Their pharmacokinetics are described in the chart below,

Table 1: Pharmacokinetics of FDA approved biologics for the treatment of Psoriasis (Al-Janabi & Warren, 2020; Blegvad et al., 2019; Galluzzo et al., 2016, 2017; Khalilieh et al., 2018; Markham, 2016, 2017; Megna et al., 2018; Pang et al., 2020; Scanlon et al., 2009; Shirley & Scott, 2016; Syed, 2017; Timmermann & Hall, 2019; Weber & Keam, 2009) .

	Ustekinumab	**Secukinumab**	**Tildrakizumab**	**Ixekizumab**	**Risankizumab**	**Guselkumab**	**Brodalumab**
Dose (mg)	0.27–2.7mg/kg	150-300 mg	0.1-10 mg/kg	160 mg	0.01-5 mg/kg	0.03-10 mg/kg	210 mg
C_{max}	3.1–14.1 µg/mL	31-62 µg/mL	2.51- 261 µg/mL	15–16 µg/ml	0.311-110 µg/mL	8.09 µg/mL	20 µg/mL
T_{max}	8.5-12 Days	6 Days	6.05-6.07 Days	4-7 Days	3-14 Days	3-6 Days	3 Days
Bioavailability	57.2%	85%	73-80%	54-90%	89%	49%	57.6%
Volume of Distribution	15.7 L	2.45-3.66 L	5.4–7.4 L	7.11 L	11.2 L	13.5 L	3.9 L
Clearance	0.465 L/day	0.19 L/Day	0.143–0.176 L/day	0.30 L/Day	0.31 L/Day	0.516 L/Day	0.28 L/Day
$t_{1/2}$	15-32 Days	25 Days	20.2-26.9 Days	13 Days	18-34 Days	12-19 Days	11 Days

1.5 Pharmacodynamics of the Biologics

Biologics approved for psoriasis are TNF- α inhibitor or Interleukin inhibitor. Among them, ustekinumab, secukinumab, tildrakizumab, ixekizumab, risankizumab, guselkumab, and brodalumab are interleukin inhibitors. On the other hand, golilumab, infliximab, certolizumab pegol, etanercept and adalilumab are TNF- α inhibitor.

Risankizumab is a monoclonal antibody that targets the p19 subunit of IL-23 by binding to it. IL-23 is responsible for increasing the activity of Th17 cell differentiation as well as increasing the production of IL-17A. By inhibiting IL-23, a very important inflammatory mediator, Risankizumab helps diminish psoriasis symptoms (Al-Janabi & Warren, 2020; Pang et al., 2020). Tildrakizumab is another biologic drug used for the treatment of psoriasis. It is a monoclonal antibody that targets the p19 subunit of IL-23 and inhibits it. Guselkumab is another biologic that has the same mechanism of action and works by inhibiting the p19 subunit of IL-23. Risankizumab, tildrakizumab, and guselkumab have the same mechanism of action (Galluzzo et al., 2017).

IL-17 is produced by Th17 cells and is responsible for the inflammation of psoriasis disease. IL-17 is responsible for producing chemokines and cytokines, which are also known as proinflammatory substances. Proinflammatory substances aggravate the symptoms of psoriasis. Brodalumab is another drug that is a human IgG2 antibody that targets IL-17 by binding to it and giving it inhibitory action. Inhibition of IL-17 will reduce the production of chemokines and cytokines by inhibiting the keratinocyte-expressed gene (Blegvad et al., 2019; Galluzzo et al., 2016). Ixekizumab and Secukinumab have a similar mechanism of action as Brodalumab (Galluzzo et al., 2017). Ixekizumab functions by inhibiting IL-17A, and it is an IgG4 antibody that is collected from rats and modified (Humanized) (Blegvad et al., 2019). On the other hand,

Secukinumab is a human IgG1 antibody that targets IL-17A and inhibits the binding of IL-17A to its receptor. By this mechanism, secukinumab decreases the production of chemokines and cytokines and reduces inflammation (Blegvad et al., 2019; Roman et al., 2015; Shirley & Scott, 2016).

Ustekinumab is another G1k monoclonal antibody drug that targets both IL-12 and IL-23. IL-12 has p35 and IL-23 has p19 subunit. A disulfide bond unites these subunits to the p40 subunit present in both of the interleukins. IL-12 is responsible for the production of Th1 cells from CD4 naïve T-cells. Th-1 cell and NK cells are responsible for the production of an interferon known as IFN-γ which has a great role in the development of psoriasis. This interferon then goes to the epidermis and there it causes proliferation of T-cell and keratinocyte. By binding to the p40 subunit of IL-12 and IL-23, ustekinumab is responsible for giving inhibitory action by not letting these two bind to the receptor (Galluzzo et al., 2017; Megna et al., 2018; Scanlon et al., 2009; Torti & Feldman, 2007).

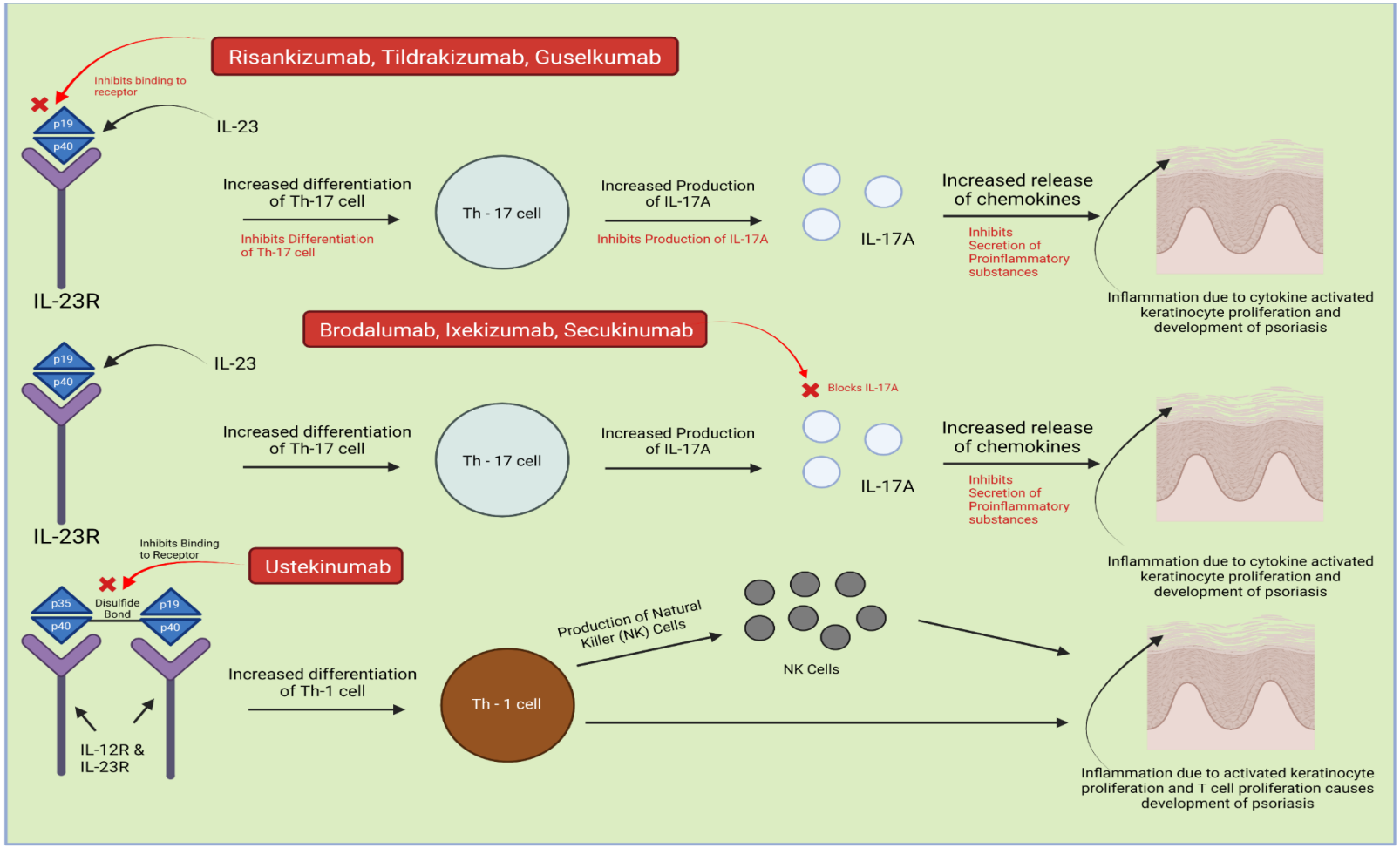

Figure 1: Pharmacodynamics of FDA approved biologics (Al-Janabi & Warren, 2020; Blegvad et al., 2019; Galluzzo et al., 2016, 2017; Megna et al., 2018; Pang et al., 2020; Roman et al., 2015; Scanlon et al., 2009; Shirley & Scott, 2016; Torti & Feldman, 2007).

Chapter 2

Methods

2.1. Data Source

For this study, data was taken from FAERS. The US Food and Drug Administration's incredible and most important adverse event reporting tool, FAERS, gets around 1.5 million reports of adverse events involving medications, medical devices, and vaccinations each year. The FAERS database keeps track of these reported events. Using appropriate MeDRA (Medical Dictionary for Regulatory Activities) keywords, these incidents are documented in the FAERS database. Adverse events that have been reported to the FAERS database are raising public awareness and assisting in the detection of drug-related safety (Mazhar et al., 2021). By looking at FDA Adverse Event Reporting System (FAERS), an adverse event-reporting database, we can observe significant amount of adverse events reported by patients, pharmaceutical industries and healthcare providers regarding the FDA-approved biologics that are used for the treatment of psoriasis. Among these adverse events, alopecia is very common. The FDA approved biologics for psoriasis can be divided into two types. One type is tumor necrosis factor alpha inhibitor (TNF-α inhibitors) and the other type is Interleukin Inhibitor.

2.2 Study Design

We have considered the biologics that provide a mechanism by inhibiting interleukin for the treatment of psoriasis and considered the terms "Psoriasis" and "Alopecia" to search for cases for each drug in the FAERS database from January 2016 to September 2022. After searching, we have taken 32890 reported cases of the seven interleukin inhibitor biologics approved for psoriasis from the FAERS database. Our study was a case/non-case study. Reporting Odds Ratio (ROR) and Confidence Interval were calculated from data that was obtained with whole database drugs

causing alopecia. We have taken docetaxel as a control to be compared with other desired drugs. It is a potent anticancer drug and has proven to cause alopecia (Fonia et al., 2017).

We included data from the FAERS database, which consists of the reported adverse events of many drugs along with the following generic names: "Ustekinumab, Secukinumab, Tildrakizumab, Ixekizumab, Risankizumab, Guselkumab, and Brodalumab." As part of the inclusion process, we took data starting from January 2016 to September 2022. We excluded all data containing a number of other suspected medicines. Using the case number, the duplicated reports were eliminated. Another method for removing repeated reports was to match the age, gender, and event date.

2.3 End points

Our end point for this analysis was “alopecia” and the end point was selected on the basis of the MedDRA terminologies.

Chapter 3

Results

3.1 Study Population

We included both males and females in our study, all ages ranging from January 2016 to September 2022. By assessing each case, we have added it to our study to look for a signal. We have determined the Reporting Odds Ratio (ROR) and Confidence Interval (CI) for patients with psoriasis and at least one alopecia-related adverse event using Rstudio. The reports of patients with psoriatic arthritis, plaque psoriasis, psoriatic arthropathy, etc. were not included. Following that, we received 32890 total cases and non-cases, with 1291 total cases—a very tiny number.

3.2 Signal for Psoriasis

In this study, we have compared FDA approved biologics to Docetaxel, which has a signal of 73.22 and a ROR of 74.60. It can be said that this anticancer drug used as a chemotherapeutic agent can cause alopecia. On the other hand, none of our biologics has a signal for alopecia based on the data collected from FAERS. The total data is given in Table 2.

Our obtained cases have been shown in the below Bar chart where X axis represents drug names and on the other hand, Y axis represents cases.

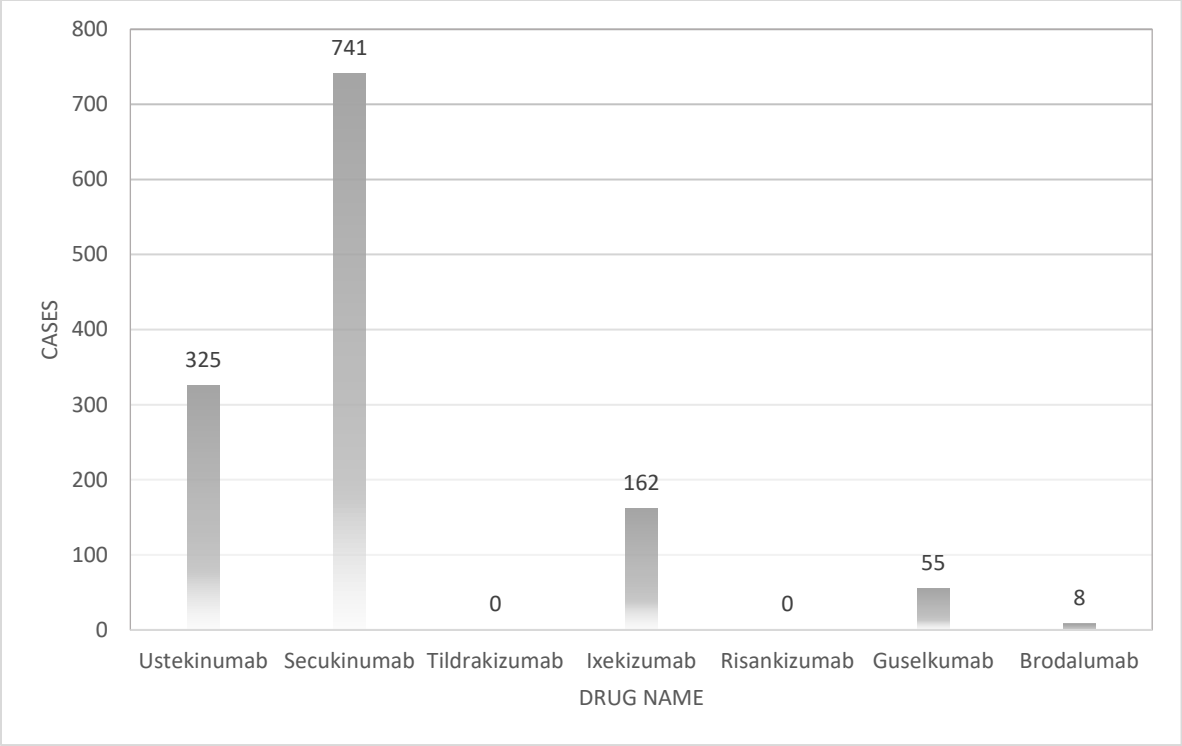

Figure 2: Obtained Cases for each Biologics shown in Column Chart

After using the data shown in table 2, we have calculated ROR and CI. If the lower bound of CI was above 1 for any drug, we have considered that a signal for alopecia. But, none of the drugs gave any signal according to our calculation. Table 3 represents the ROR and CI for each drug. After calculating ROR and CI, we have represented the data in a forest plot. Figure 1 shows the forest plot, ROR, and CI of drugs enlisted on table 2 & 3.

Table 2: Represents total Cases and Non Cases found from FAERS database for the FDA approved biologics that are interleukin inhibitor used in the treatment of psoriasis along with Docetaxel.

Drugs	**Cases**	ROR	**95% CI**
Ustekinumab	325	0.87	(0.78, 0.97)
Secukinumab	741	0.96	(0.89, 1.03)
Tildrakizumab	-	-	-
Ixekizumab	162	1.01	(0.87, 1.18)
Risankizumab	-	-	-
Guselkumab	55	0.59	(0.46, 0.77)
Brodalumab	8	0.91	(0.46, 1.83)
Docetaxel	19531	90.17	(88.49, 91.89)

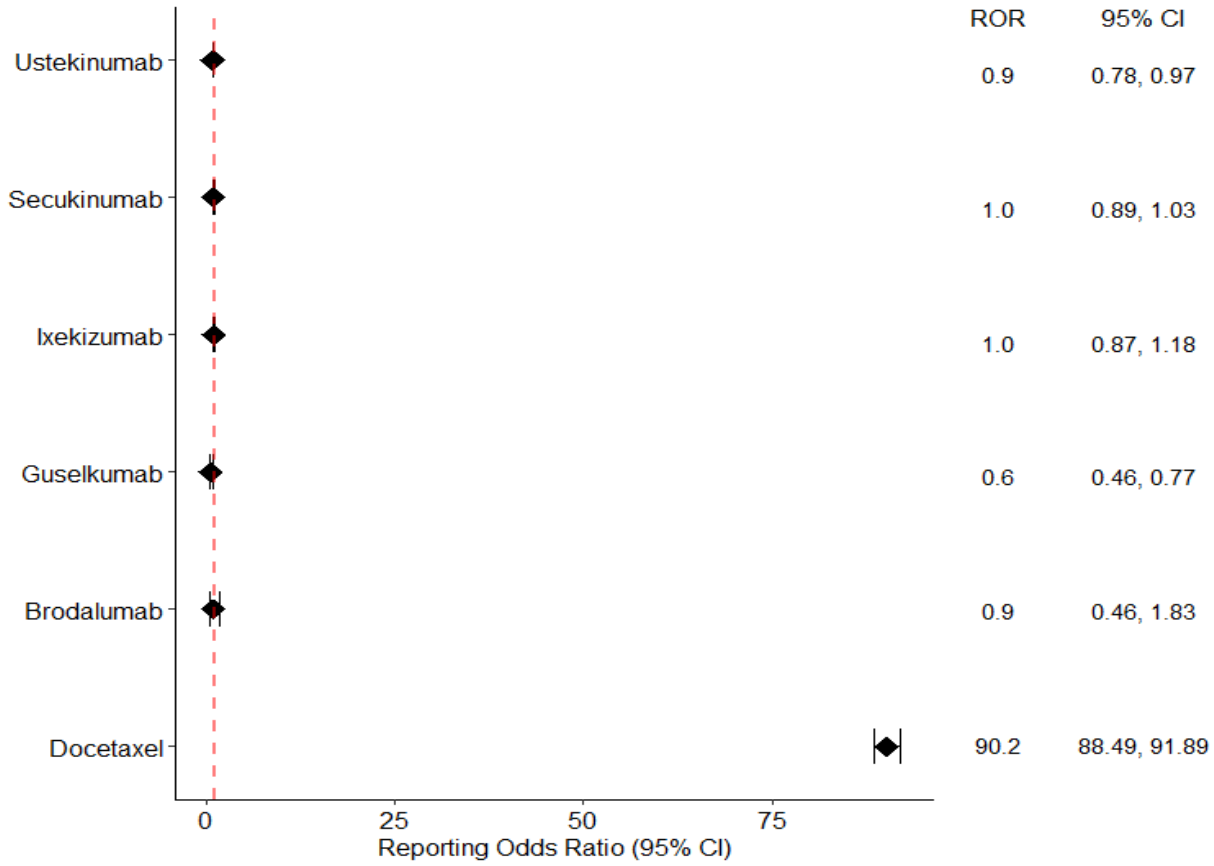

Figure 3: Represents Forest Plot, ROR and CI calculated from data collected from FAERS database for the FDA approved biologics that are interleukin inhibitor used in the treatment of psoriasis along with Docetaxel.

Chapter 4

Discussion

Based on our meta analysis of the data collected from FAERS, we did not find any potential signals for any of the interleukin inhibitor drugs: Ustekinumab, Secukinumab, Tildrakizumab, Ixekizumab, Risankizumab, Guselkumab, and Brodalumab. This means none of these drugs cause alopecia based on the data.

However, according to a case report, a patient with psoriasis was treated with ixekizumab and developed alopecia, which declined after discontinuation of ixekizumab, which is a IL-17A inhibitor. It was also mentioned that, TNF-α inhibitors have association with alopecia and IL-17A inhibitors such as Brodalumab, Ixekizumab and Secukinumab has association with alopecia since it is responsible for decreasing TNF- α and as a result, IFN-gamma gets increased which is responsible for the cause of psoriasis (Tan et al., 2021).

In another case study, it was discovered that, patient with psoriasis vulgaris was getting treated with secukinumab. She developed alopecia, which was still continuing when the drug was switched to brodalumab. Both of these drugs are IL-17A inhibitors; for this reason, the result did not change. When again the drug was switched, but this time, Ustekinumab was given and alopecia was diminished (Yajima et al., 2019).

In another study, it has been found that, Tildrakizumab, an IL-23 inhibitor, is responsible for improving the symptoms of LPP, which is a lymphocytic cicatricial alopecia. But no other alopecia reports regarding use during treatment for psoriasis were found. Ustekinumab is an IL-12/23 inhibitor, and it is reported to improve alopecia. In three case studies by (Aleisa et al., 2019), it is recommended to use ustekinumab to treat Alopecia Areata (AA). There were three patients with AA, and after taking ustekinumab, all of them recovered and produced hair. On the other hand, in

another case by (Hosokawa et al., 2019), patient with psoriatic alopecia was found to have no improvement when given brodalumab, but when switched to guselkumab, the patient fully recovered (Trindade de Carvalho et al., 2020),.

Our investigation revealed no evidence of a signal, indicating that there is no connection between interleukin inhibitors and alopecia. For IL-23, IL-17A, and IL-12/23 inhibitors, the ROR and CI give no signal. As a result, we want to state that, there is no association between adverse events like alopecia and IL inhibitor drugs used for the treatment of psoriasis.

According to numerous studies, alopecia occurs after using the IL-17A inhibitors Brodalumab, Ixekizumab, and Secukinumab. To discover a connection between alopecia and IL-17A inhibitors, additional analysis and research are required. Ustekinumab, Guselkumab, and Tildrakizumab, on the other hand, lessen alopecia. It is important to be aware of their use in the management of psoriatic alopecia. Our study did not explain the relationship between alopecia and risankizumab. More research is required to identify a link with alopecia because interleukin inhibitors are primarily new medications.

Treatment of alopecia is complicated due to a lack of data and poor results. Common treatments for alopecia include the use of corticosteroids and immunotherapy. The use of corticosteroids improves efficacy while decreasing toxicity. Statins have already been offered as a treatment for a number of dermatologic problems, including AA. They are currently used to prevent atherosclerosis and cardiovascular morbidity, but there is growing evidence that they may also have immunomodulatory properties. Patients with alopecia areata improved with ezetimibe and simvastatin medication, as well as the maintenance of intralesional corticosteroid injections. Minoxidil is a hair growth promoter that is used to treat alopecia in conjunction with topical

anthralin. When used after corticosteroid treatment, minoxidil can help reduce alopecia during use for the treatment of AA (Trüeb & Dias, 2017).

Chapter 5

Conclusion

TNF-α inhibitors have been studied a lot and proved to have association with Psoriasis and alopecia. Our concern was raised to find the association with other biologics, which are interleukin inhibitors, if they have any association with alopecia in the treatment of psoriasis. Based on the data collected from FAERS from 2016–2022, we have calculated ROR and CI for seven biologics that are interleukin inhibitors. We did not find any association between the drugs and alopecia during the treatment of psoriasis.

Still, more long term study is required to determine the safety of these drugs for the treatment of psoriasis. As several studies have already reported observing alopecia during the use of IL-17A inhibitors, these drugs should be carefully used and patients should be monitored. When it comes to psoriasis, "alopecia" is a pretty prevalent phrase. Biologics that do not cause or diminish alopecia should be used for treatment. This should be treated because an adverse event might have an impact on a patient's lifestyle, possibly delaying recovery.

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