TNF-α Inhibitor-induced Alopecia in Psoriatic Disease Patients: A Pharmacovigilance Study

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the

requirements for the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a 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 "TNF Inhibitor-induced Alopecia in Psoriatic Disease Patients: A Pharmacovigilance Study" submitted by Halima Afroza (19146018) of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 9 March, 2023.

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

The objective of this study was to investigate the association between TNF-alpha inhibitors and alopecia cases in psoriasis patients reported in the Food and Drug Administration Adverse Event Reporting System (FAERS) database. We performed a disproportionality analysis (case/non-case method) to examine the relationship between the development of alopecia by the use of TNF-alpha inhibitors from January 2016 to September 2022. Cases were all alopecia reports, whereas non-cases were all the other reports reported throughout the research period. We calculated the reported odds ratio (ROR) and corresponding 95% confidence interval (CI) to assess disproportionality signals and determine the relationship between alopecia and TNF-alpha inhibitors. As a positive control, docetaxel was used. Our study found that only infliximab and certolizumab pegol showed signal for alopecia. Additional study into alopecia connected with TNF-alpha inhibitors usage in psoriasis patients is required as disproportionality signals may have been altered by stimulated reporting or nocebo effect.

Keywords: Psoriasis; alopecia; TNF-α inhibitor; FAERS; ROR; disproportionality analysis.

Dedication

Dedicated to my parents and grandparents

Acknowledgement

First and foremost, I thank the Almighty for providing me with countless blessings and the strength to accomplish this project. Aside from my contributions, the completion of my project is heavily reliant on the support and guidance of several people. I would like to express my thanks to everyone who helped me finish my project.

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List of Acronyms

ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the Curve
AZA	Azathioprine
CI	Confidence Interval
CRP	C-reactive Protein
CVD	Cardio Vascular Disease
CXCR3	Chemokine Receptor
ESR	Erythrocyte Sedimentation Rate
FAERS	FDA Adverse Event Reporting System
FcP	Fusion Proteins
FDA	Food and Drug Administration
IFN-γ	Interferon Gamma
IL	Interleukin
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NF-kB	Nuclear Factor Kappa B
ROR	Reporting Odds Ratio
sTNF	Soluble-Tumor Necrosis Factor
sTNFR	Soluble Tumor Necrosis Factor Receptor
TNF	Tumor Necrosis Factor
TNFRs	Tumor Necrosis Factor Receptor
VD	Volume of Distribution

Chapter 1

Introduction

1.1 Psoriasis

Psoriasis is a chronic immune-mediated and inflammatory skin condition associated with erythematous plaques and silvery scales, which affects almost 2-3% population globally (Wang et al., 2014). It is indicated by a significant elevation in proliferation and inadequate differentiation of the epidermal skin. Also, there is an elevation in cutaneous blood circulation and infiltration of the leukocytic papillary dermis and epidermis (Gudjonsson & Elder, 2007). Prevalence is lower among Asians and some Africans, and as high as 11% among Caucasians and Scandinavians (Rendon & Schäkel, 2019). 1-2% of the American population is affected by psoriasis, which costs about three billion dollars each year (Gudjonsson & Elder, 2007). Its onset age has a bimodal distribution in men as peaks had been seen at 30-39 and 60-69 years of age and in women a decade earlier (Rodríguez-Fernández et al., 2022).

Psoriasis usually affects the skin, but can also affect the joints and has been linked to several diseases. Since inflammation does not remain confined to the skin, psoriasis cannot be recognized as a dermatological disease only but is also theorized as a systemic disease. In comparison to control subjects, there is more prevalence of CVD, diabetes, hypertension, coronary plaques, and hyperlipidemia in patients with psoriasis (Rendon & Schäkel, 2019). Consecutively, they experience more depression, suicidal thoughts, arthritis, and lymphoma than the general population (Gottlieb et al., 2008). Inflammation in the joints due to psoriasis results in the formation of psoriatic arthritis. Moreover, psoriatic inflammation can also affect the nails and as per the case reports majority of the psoriasis patients have to deal with this (Rendon & Schäkel, 2019). Even though psoriasis has been suggested to be an autoimmune illness but the underlying autoimmune antigens are yet to be discovered conclusively. Physical

and mental stress, trauma, harsh weather, medicines, and herbs are all major risk factors for inducing psoriasis (Kalam et al., 2022).

The mortality rate for psoriasis is low approximated at 0.64 fatalities per 100,000 patients in the USA. However, erythrodermic psoriasis and generalized pustular psoriasis are linked with a higher likelihood of morbidity and death. In the pathogenesis of psoriasis major roles are played by T-cells, antigen-presenting dendritic cells, and networks of cytokine. Excess TNF-alpha production can aggravate inflammatory diseases like psoriasis (Vergou et al., 2011). Dendritic cells when activated travel from the skin to lymph nodes for presenting antigens and activating responses of the T-cell. TNF-alpha is essential in the pathogenesis of psoriasis. TNF-alpha promotes the nuclear factor: κB signal pathway, which influences lymphocyte's and keratinocyte's lifespan, proliferation, and anti-apoptotic actions. TNF-alpha causes keratinocytes to create IL-8, which promotes the production of microabscesses in psoriasis by increasing neutrophil recruitment (Ogawa et al., 2018).

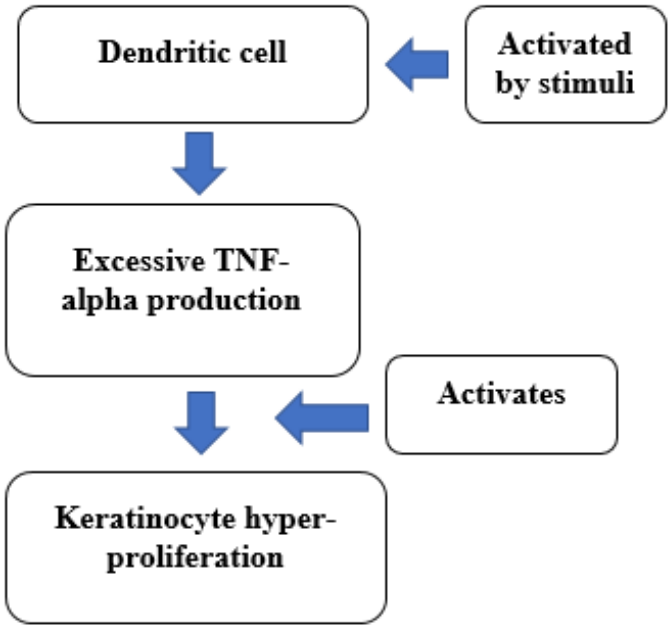

Figure 1: Pathogenesis of TNF-alpha induced psoriasis

1.2 Biologics (anti-TNF drugs) Approved by FDA for Psoriasis

Proteins generated from recombinant DNA technologies, blood, complete human cells and hybridomas are examples of biologic agents (Winterfield et al., 2005). Biologics are distinct from systemic therapies as particular inflammatory pathways are targeted by them and are given subcutaneously or intravenously on varied weekly regimens (Rendon & Schäkel, 2019).

Table 1: FDA Approved TNF- alpha inhibitors (Abbott Laboratories, 2002; Immunex Corporation, 1998; Janssen Biotech, 1998; Janssen Biotech, 2009; UCB, 2008)

Drug	**Adalimumab**	**Golimumab**	**Infliximab**	**Certolizumab pegol**	**Etanercept**
Trade name	Humira	Simponi	Remicade	Cimzia	Enbrel
Therapeutic Target	TNF-α	TNF-α	TNF-α	TNF-α	TNF-α
Indication	Psoriatic arthritis & plaque psoriasis	Psoriatic arthritis	Psoriatic arthritis & plaque psoriasis	Psoriatic arthritis	Psoriatic arthritis & plaque psoriasis
Developmental status	Approved in 2002	Approved in 2009	Approved in 1998	Approved in 2008	Approved in 1998

1.3 Alopecia and Biologics

Biologic drugs have been effective in treating different dermatological diseases by acting on particular targets of the immune system (Munera-Campos et al., 2018). Psoriasis occurs due to alterations in the pathway of TNF-α (Tan et al., 2021). For over two decades, biologics have been successfully used for the treatment of psoriasis. Currently, there are five TNF inhibitors approved by the FDA for the treatment of psoriatic diseases. Monoclonal antibodies include- adalimumab, golimumab, and infliximab. Etanercept and Certolizumab pegol are fusion

proteins and polyethylene glycol-conjugated fragments of mAb, respectively. TNF-α inhibitors are the first biologics licensed for psoriasis treatment, and for moderate to severe psoriatic patients, they constitute a strong choice because of their outstanding effectiveness and promising safety profile (Campanati et al., 2019).

The application of mAbs in psoriasis is recommended when (i) it cannot be effectively controlled by the application of oral or phototherapy treatment options, (ii) patients having accelerated regrowth (3 months or prior) after discontinuing any treatment, (iii) when systemic conventional drugs are required in higher doses which may lead to adverse effects and (iv) In individuals with comorbidities that prevent the usage of systemic medicines like methotrexate/cyclosporine (Rodríguez-Fernández et al., 2022).

Although biologics have shown a good safety profile but systemic and inflammatory diseases associated with them have been reported (Munera-Campos et al., 2018). Furthermore, different anti-TNF agents show multiple side effects for example: adalimumab has been linked with heart failure, malignancies, sinusitis and nasopharyngitis. Side effects associated with golimumab include: infections and carcinoma in the cutaneous squamous cells. Infliximab has been reported to cause infection in the upper respiratory tract, fatigue and headache. Nasopharyngitis and carcinoma have been associated with certolizumab pegol. Lastly, etanercept has infection, malignancy and heart failure as side effects (Rodríguez-Fernández et al., 2022).

Alopecia is a severe dermatological condition that leads patients to lose all or a portion of the hair on their scalp and, in some cases, on their bodies. It is an inflammatory disorder that impacts hair growth over time. It is neither life-threatening nor unpleasant, however, there may be skin irritation and physical issues resulting in the loss of eyebrows and eyelashes (Merino De Paz et al., 2020). According to one research, 3.3% of patients on TNF-inhibitors have hair

fall, which might be a significant cause for quitting therapy (Antonella, 2014). Additionally, in 2017 a number of cases reported the link between alopecia with the administration of TNF-α inhibitors. There were also cases reporting the generation of alopecia areata among psoriasis patients receiving IL-17 inhibitors (Tsai & Tsai, 2020). Treating psoriatic patients with anti-TNF drugs seldom creates scalp psoriasiform-like lesions that resemble alopecia (Doyle et al., 2011). This has been increasingly apparent in recent years as a consequence of scholarly papers and post-marketing surveillance by the FDA (Antonella, 2014). Also, French Pharmacovigilance Database performed disproportionality analyses where TNF-alpha inhibitor-related alopecia was identified (Béné et al., 2014).

The proposed pathophysiology of TNF inhibitor-induced alopecia is: TNF suppression promotes the synthesis of interferon-alpha by plasmacytoid dendritic cells, thereby enhancing the release of chemokine ligands 9, 10 and 11. Again, it increases the CXCR3+ T cell activation. Th17 cells secreted by IL-17A or IL-22 and Th1 cells secreted by IFN-γ are CXCR3+ which are seen to a greater extent in psoriatic lesions (Craddock et al., 2016).

Thus, the inhibition of TNF-alpha causes excess release of interferon-alpha resulting in the response of T-cells to be stimulated and amplified and inducing a psoriasiform reaction (Tan et al., 2021). Despite the numerous accounts of alopecia incidences in psoriasis patients taking TNF-alpha inhibitors that have been reported in journals and post-marketing surveillance, there are only a small number of clinical studies in which they are directly examined, making it difficult to assess their prevalence. It is additionally difficult to determine if some anti-TNF medicines are more likely than others to produce alopecia (Antonella, 2014). There remain controversies regarding alopecia as an adverse effect due to the use of TNF-α inhibitors. So, our study aimed to assess the FAERS database and detect whether alopecia is actually induced in psoriasis patients by taking TNF-alpha inhibitors.

1.4 Pharmacokinetics of the Biologics

Table 2: Pharmacokinetics of anti-TNF drugs (Abbott Laboratories, 2002; Gottlieb, 2010; Hemperly & Vande Casteele, 2018; Immunex Corporation, 1998; Janssen Biotech, 1998; Janssen Biotech, 2009; Rodríguez-Fernández et al., 2022; UCB, 2008)

Property	Adalimumab	Golimumab	Infliximab	Certolizumab pegol	Etanercept
Dosage	80 mg loading dose + 40 mg once every two weeks	50 mg or 100 mg, once every four weeks	5 mg Week 0, 2, 6 followed by once every eight weeks	400 mg, week 0, 2, 4 followed by 200 mg every other week	25 mg weekly two times or 50 mg every week
Absorption	C_{max}[1] = 4.7 ± 1.6 μg/mL	C_{max} = 2.5 μg/mL	C_{max} = 118 μg/mL	C_{max} = 43-49 μg/mL	C_{max} = 1.1 ± μg/mL
	T_{max}[2] = 4-7 days	T_{max} = 2-6 days	N/A	T_{max} = 2-6 days	T_{max} = 69 ± 34 hours or 2-3 days
	Bioavailability = 64%	Bioavailability = 53%	Bioavailability = 92%	Bioavailability = 80%	Bioavailability = 58%
Distribution	V_D[3] = 4.7 to 6.0 L	V_D = 24.9 ± 1.04 L	V_D = 3 - 4.1 L	V_D = 6-8 L	V_D = 5.49 L
Metabolism	Metabolic pathway not yet studied.	Metabolic pathway not yet characterized	Metabolic pathway not yet characterized	Metabolic pathway not yet characterized	Metabolic pathway not yet characterized
Excretion	Half- life = 2 weeks	Half- life = 2 weeks	Half- life = 2 weeks	Half- life = 2 weeks	Half- life = 102 ± 30 or hours 2 weeks
	Clearance = 12 mL/hour	Clearance = 4.9-6.7 mL/day	Clearance = 15.2 mL/hour	Clearance = 14-21 mL/hour	Clearance = 160 ± 80 mL/hour

[1] Maximum plasma concentration

[2] Time to reach C_{max}

[3] Volume of distribution

1.5 Pharmacodynamics of the Biologics

TNF-α is a critical cytokine responsible for the pathogenesis of psoriasis and other psoriatic comorbidities. Despite having an identical target, all the anti-TNF alpha drug has distinct structural and pharmacological properties. Fully understanding them is a crucial differentiator in motivating clinicians to individualize therapy in every clinical context, since varied pharmacodynamics indicate distinct adverse effects (Campanati et al., 2019).

On the basis of mechanism of action biologics for psoriasis can be classified into two main categories- anti-cytokines and T-cell targeting biologics. Anti-cytokines target Tumor Necrosis Factor alpha (TNF-α) and block their interactions with receptors (Wang et al., 2014).

When TNF-producing cells are activated under certain circumstance, it expresses tmTNF (membrane-bound TNF) in the cell surface and releases sTNF (soluble-TNF). The tmTNF and sTNF are capable of binding to TNFR1 or TNFR2 and sTNFR1 or sTNFR2 (TNF receptor). This initiates signaling pathways that activates NF-kB and inflammation. Apoptosis is another possibility. In the presence of TNF antagonist tmTNF and sTNF binding to their receptor is restricted and reverse signaling is instigated which ultimately results in cytokine suppression (Vergou et al., 2011).

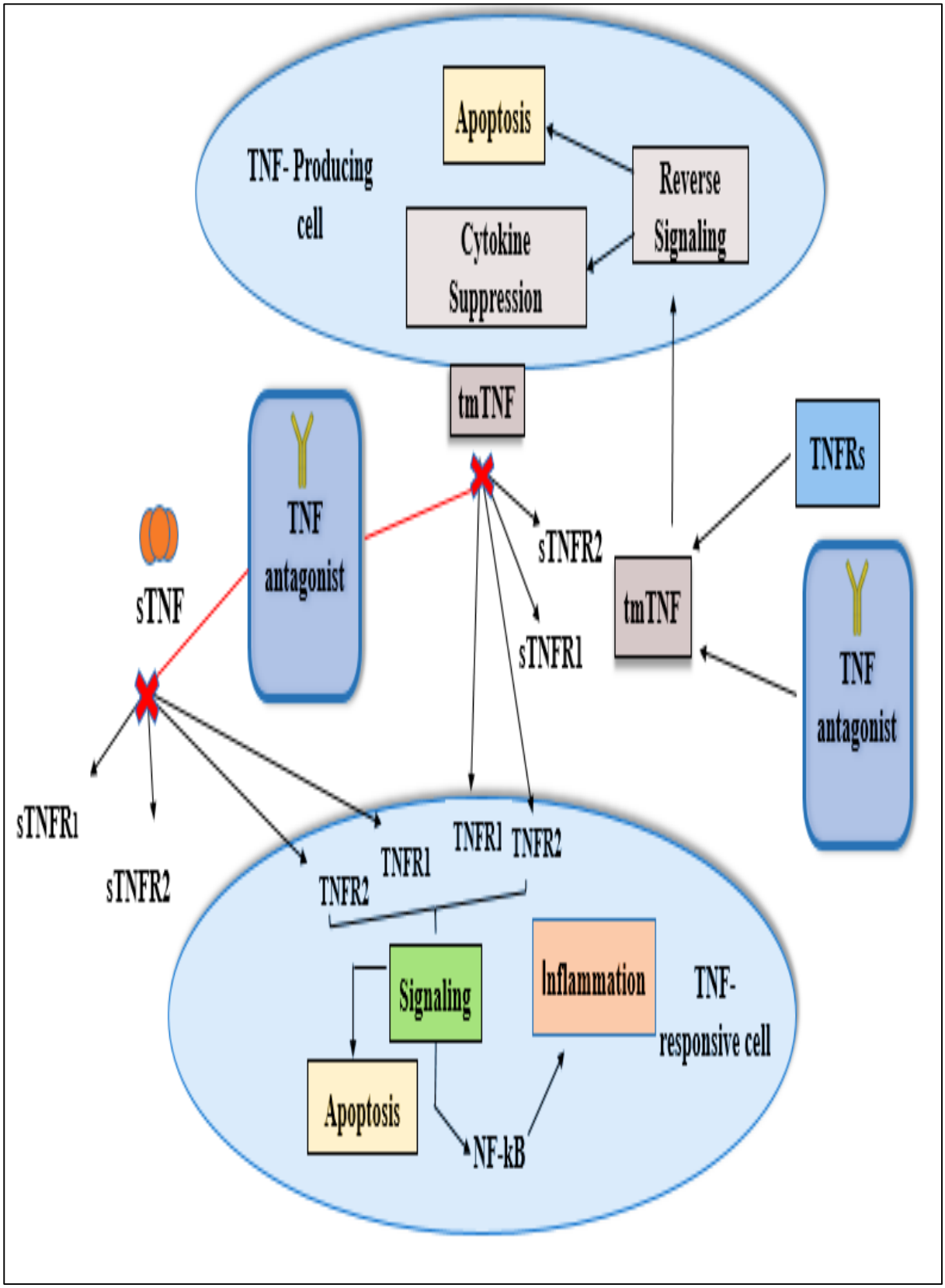

Figure 2: Pathways for TNF synthesis, receptor binding, and signaling (Vergou et al., 2011)

1.5.1 Mechanism of action:

Adalimumab

TNF is a cytokine that occurs naturally and has a role in basic inflammatory and immunological responses. Adalimumab binds selectively to TNF-α and inhibits interaction with TNF receptors in the cell surface. In the presence of complement, adalimumab also lyses surface tumor necrosis factor-expressing cells in vitro. Adalimumab has no effect on lymphotoxin binding or inactivation (TNF-beta). In psoriasis patients, increased levels of TNF are seen in synovial fluid, which is a hallmark of the disease. Treatment with adalimumab reduces the thickness of epidermal skin and inflammatory cells infiltration in psoriasis patients (Abbott Laboratories, 2002).

Golimumab

Golimumab is a humanized mAb that selectively binds to TNF-α. This interaction stops TNF-alpha from binding with the receptors, thus limits the pharmacological activity of TNF-alpha. There was no indication of golimumab antibody-neutralizing lymphotoxins. Patients suffering from inflammatory diseases that are chronic like- psoriatic arthritic, there is an increase in the levels of TNF-α seen. Golimumab modulates in vitro pharmacological effects initiated by TNF in various bioassays, which include preventing leukocyte infiltration and cytokine secretion (Janssen Biotech, 2009).

Infliximab

Infliximab is a mAb that selectively binds to transmembrane TNF-α and soluble TNF-α. It has a great affinity for disrupting pro-inflammatory pathway signaling. The antibody's binding to TNF-α, stops the TNF-α from associating itself with its receptors. TNF-β is not neutralized by infliximab. Blocking of TNF-α causes downregulation of pro-inflammatory cytokines and

reduces migration of lymphocyte/leukocyte to the inflammation sites. TNF-inhibitory effects were seen in human fibroblasts, epithelial cells, and neutrophils (Janssen Biotech, 1998).

Certolizumab pegol

Certolizumab pegol suppresses the downstream inflammatory condition by targeting TNF-alpha activation with greater affinity. It binds and neutralizes membrane and soluble portions of TNF-α. Certolizumab pegol does not induce cytotoxicity due to the lack of Fc region. TNF-α inhibition is dose-dependent, and it shows no action against TNF-β. Cerolizumab pegol also has the advantage of being more substantially disseminated into inflammatory cells than other TNF-α inhibitors like- adalimumab and infliximab due to PEGylation (UCB, 2008).

Etanercept

Etanercept is a TNF-binding dimeric soluble version of the receptor (p75 TNF). TNF-alpha and TNF-beta binding with the TNFRs in the cell surface is inhibited by etanercept rendering TNF physiologically inert. Substantial complexes of this drug with TNF-alpha were not identified in *in vitr*o investigations and cells that express transmembrane TNF are not lysed in the availability or unavailability of complement (Immunex Corporation, 1998).

Table 3: Pharmacodynamics of anti-TNF drugs (Abbott Laboratories, 2002; Acosta-Felquer et al., 2016; Immunex Corporation, 1998; Janssen Biotech, 1998; Janssen Biotech, 2009)

Drug	Structure	Pharmacodynamics
Adalimumab	Monoclonal antibody	Decreases CRP, ESR and serum cytokines level. Reduces matrix metalloproteinases level in the serum which is responsible for causing cartilage destruction.
Golimumab	Monoclonal antibody	Decreases inflammation in patients with psoriatic arthritis by inhibiting cytokine (TNF-α) activity.
Infliximab	Monoclonal antibody	Cascade of Pro-inflammatory signaling is disrupted. In patients with plaque psoriasis reduction in the epidermal thickness and infiltration of inflammatory cell is seen.
Certolizumab pegol	Pegylated antigen-binding fragment	IL-1 beta production induced by lipopolysaccharide is inhibited. Non-apoptotic cell death is induced via TNF-α transmembrane signaling.
Etanercept	Fusion protein	Etanercept binds to TNF selectively, modulating biological processes caused or controlled by TNF which includes cytokine level in serum and matrix metalloproteinase-3.

Chapter 2

Methods

2.1 Data Source

The data from FAERS database were used to conduct this observational and pharmacovigilance study. The FAERS database contains spontaneous reports of adverse events which are submitted to US FDA by medical professionals, manufacturers and consumers. This database is accessible to the public and contains more than 20 million records. FAERS database includes demographic, outcome, suspected drug, reporting nation and interacting drugs information. The possible AEs in the FAERS database are reported in accordance with the MedDRA. The public can get quarterly data on all the adverse occurrences that are reported to the FDA (Kvist et al., 2021). As FAERS database was used anonymously there was no need for ethical review (Wu et al., 2021). There were 25,389,509 total reports of adverse events that were listed in FAERS database till January 2023. The drugs included in this study were, Adalimumab, Golimumab, Infliximab, Certolizumab pegol and Etanercept.

2.2 Study Design

In this study data from January 2016 to September 2022 were taken from the FAERS database. The FAERS database consisted of all the reported adverse events of the drugs with the following generic names: “Adalimumab”, “Infliximab”, “Golimumab”, “Certolizumab pegol” and “Etanercept”. We excluded all the data where a number of other suspected drugs were present. In our study we included all of the reported cases and excluded some reports that were submitted several times to the FDA, each time with new information. As a result, duplicate reports were eliminated by case number, and the most recently issued version was included in the research (Teng et al., 2019). Another way through which duplicated reports were removed

was performed by matching the age, sex and event date. All the cases where alopecia was reported in psoriasis patients taking TNF-alpha inhibitors were identified.

2.3 Endpoints

The analysis was carried out with alopecia as the endpoint. The endpoints were specified using MedDRA preferred terminologies.

2.4 Statistical Analyses

We conducted a disproportionality analysis using case/non-case method to estimate reporting odds ratio (ROR) and its 95% confidence intervals. The case/non-case method assesses the disproportionality of a particular medicine (in our study, TNF-alpha antagonist) and a specific ADR (in this case, alopecia) in a pharmacovigilance database. It is a validated technique for detecting safety signals. Cases are all reports corresponding to the ADR of interest (here, alopecia), whereas non-cases are all reports of ADRs apart from the ADR of interest over the same research period (Béné et al., 2014).

Furthermore, the disproportionality analysis was used to confirm whether the TNF-alpha inhibitors induce alopecia more frequently than alopecia reported with other drugs in the FAERS database. R software was used for both statistical analyses and data management. We estimated the ROR for every included focused drug (adalimumab, infliximab, golimumab, certolizumab pegol and etanercept) to investigate the possible drug-AE (alopecia) connections and reported cases of alopecia. The ROR was determined using a 2×2 contingency table in which all reports are categorized by two factors for each adverse event (alopecia) and for each focused drug (Sato et al., 2020). The ROR assesses the degree of disproportionality; if the ROR = 1, represents that there is no signal, indicating that the AEs of interest is reported similarly with the drug of concern as with other medicines. Whereas, if ROR <1, there would not be any signal either, suggesting that AE is less common with the drug of concern compared to other

drugs. Conversely, if ROR > 1 it indicates the presence of signal and larger the ROR value higher the disproportionality (Faillie, 2019). The adverse events were regarded to be substantially more frequently reported after the use of focused drugs in comparison to reports of the exact adverse event during the usage of every other drugs when the lower bound of the 95% CI for the adjusted ROR was above 1 (Sato et al., 2020). Additionally, ROR of docetaxel was also estimated as a positive control to compare the signals with the drugs of interest (adalimumab, golimumab, infliximab, certolizumab pegol and etanercept).

Chapter 3

Result

3.1 Signal for Alopecia

The RORs (95% Cl) for TNF-alpha inhibitors induced alopecia were, in ascending order: etanercept (ROR, 0.60; 95% Cl, 0.56-0.64), golimumab (ROR, 0.84; 95% Cl, 0.72-0.97), adalimumab (ROR, 0.97; 95% Cl, 0.93-1.02), infliximab (ROR, 1.19; 95% Cl, 1.09-1.30) and certolizumab pegol (ROR, 1.36; 95% Cl, 1.24-1.49) when compared to the whole FAERS database. We identified that, certolizumab pegol and infliximab gave significant signals for alopecia; on the contrary, adalimumab, golimumab and etanercept did not give any significant signal. Later on, we discovered disproportionality signals for AE of interest (alopecia) for certolizumab pegol. We compared the drug that gave the strongest signal with the whole class of drugs by restricting it to only one indication. Then we selected docetaxel as the control drug (ROR, 90.17; 95% Cl, 88.49- 91.89) without restricting indication to compare it with the severity of alopecia induced by drugs of interest. Docetaxel is an anti-cancer medication in which alopecia is a consistent finding and is regarded as second most severe side effect (Martín et al., 2018).

Table 4: Disproportionality analysis of TNF-alpha

Drugs	Cases	All other drugs cases	ROR (95% Cl)
Adalimumab	1932	109926	0.97 (0.93, 1.02)
Infliximab	479	111379	1.19 (1.09, 1.30)
Golimumab	164	111694	0.84 (0.72, 0.97)
Certolizumab pegol	466	111392	1.36 (1.24, 1.49)
Etanercept	881	110977	0.60 (0.56, 0.64)
Docetaxel	19531	92327	90.17 (88.49, 91.89)

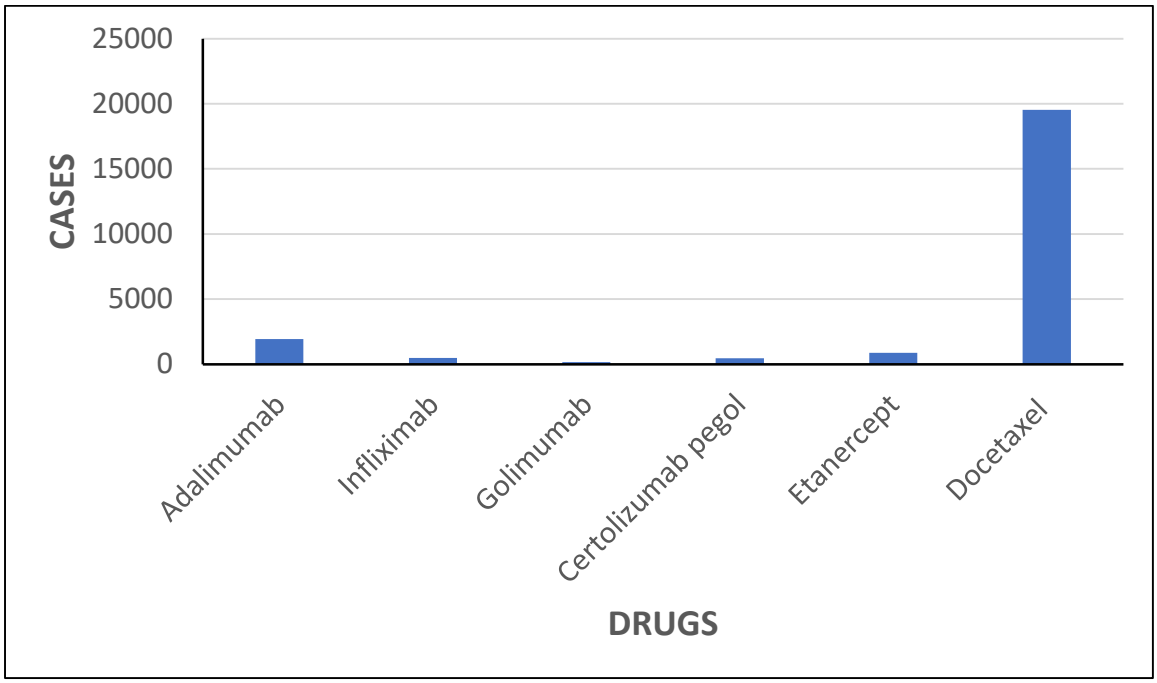

Figure 3: Column graph representing the number of cases of alopecia

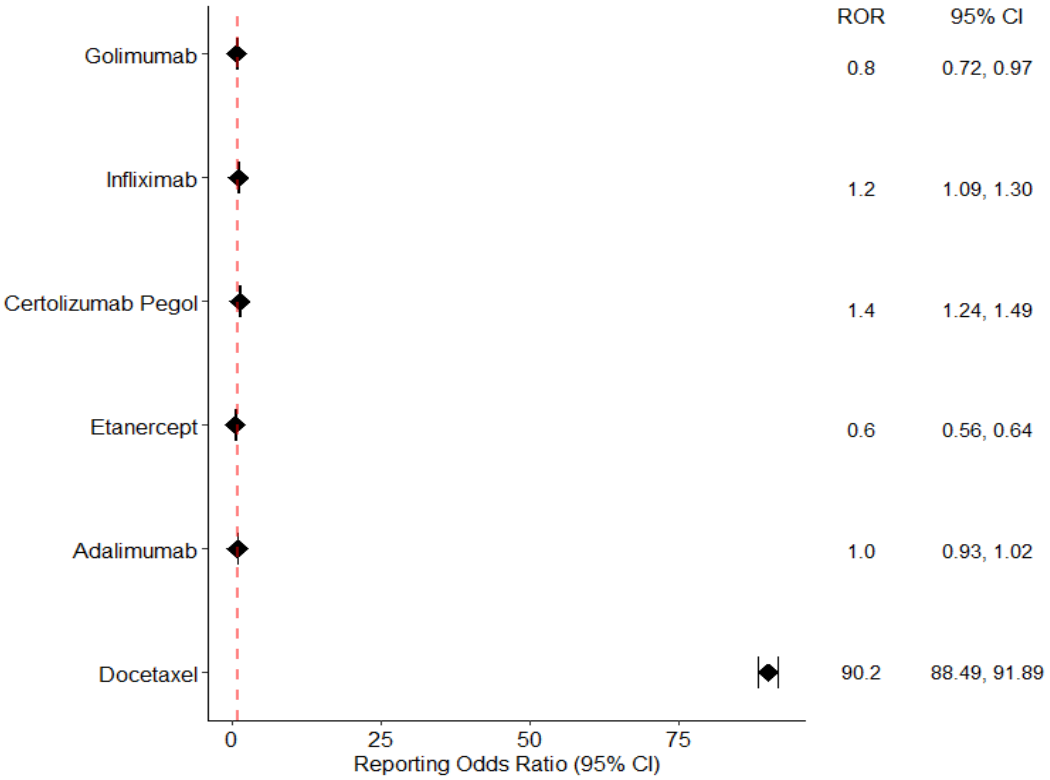

Figure 4: Forest plot of TNF-alpha inhibitors and docetaxel associated alopecia

Chapter 4

Discussion

The most prevalent chronic and relapsing type 1 autoimmune disorder mediated by skin T-cells is psoriasis. In healthy skin, it takes about one month for new skin cells to emerge from deeper layers and reach the skin's upper surface. However, in psoriasis, this process is finished in just a few days, causing a buildup of dead skin cells, the development of a thick, scaly layer, and the induction of keratinocyte hyperproliferation, a psoriasis-specific feature (Rahman et al., 2012).

Alopecia in individuals exposed to TNF-alpha inhibitors has been documented in clinical studies prior to their marketing. This AE has appeared in the monographs of French and foreign products. Nonetheless, there have only been limited reported cases and brief case series of TNF-alpha inhibitors related alopecia published in the scientific literature. Most occurrences were assumed to be coincidental owing to exposure to other medicines known to trigger alopecia (including MTX) and active underlying illness like psoriasis. TNF-alpha inhibitors are ineffective in treating alopecia areata. One proposed reason is that TNF-alpha is merely one of several cytokines engaged in the complicated and poorly understood pathophysiology of the disease (Béné et al., 2014).

Pharmacovigilance is essential to guarantee that clinicians and patients have adequate information in order to make decision when selecting a medicine for treatment (Härmark & Van Grootheest, 2008). FAERS database is a publicly available pharmacovigilance database regulated by the FDA. We attempted to assess the disproportionality signals for alopecia linked with TNF-alpha antagonist's usage. With the increased use of biologics, TNF-alpha inhibitors-related adverse events have piqued the interest of healthcare professionals, as well as the

general public and the press. In our study, drugs with identical indications were used for sensitivity analyses, and a comparison between five FDA-approved TNF-alpha inhibitors and docetaxel was conducted.

Furthermore, our study revealed evidence of a possible link between infliximab and certolizumab pegol with inducing alopecia while ruling out the potential of stimulated reporting or biased reporting owing to the nocebo effect. However, we did not find a disproportionality signal for alopecia with adalimumab, golimumab and etanercept. Due to small amount of cases of alopecia with certolizumab pegol, the significant ROR reported with this drug requires proper interpretation. Additionally, we tried to evaluate the disproportionality signal of docetaxel which is a cytotoxic agent that can permanently destroy hair follicles, and severe alopecia has been documented in people treated by it (Martín et al., 2018). We found out that, docetaxel had a statistically significant link with alopecia. Moreover, in comparison to docetaxel, TNF-alpha inhibitors (infliximab and certolizumab pegol) showed very less signal of alopecia cases.

In summary, our findings suggested that out of five TNF-alpha inhibitors only infliximab and certolizumab pegol showed signals for alopecia. Thus, more research is needed to determine whether these drugs increase the risk of alopecia or not.

Chapter 5

Limitations

FAERS cannot demonstrate a causal association between a medication and an ADR. Significant bias may develop as a result of ADRs being reported spontaneously and voluntarily. Reporting practices may be influenced by media interest and the current ADRs published in the literature (Patek et al., 2020). TNF-alpha inhibitor-induced alopecia is an uncommon and unidentified ADR compared to the other ADRs generated by these biologics. So, we might speculate that alopecia induced by TNF-alpha antagonists is undetected or underreported in comparison to other TNF-alpha inhibitor-induced ADRs. Thus, the RORs of this analysis might well be underestimated under this scenario. Additionally, other causes that can induce alopecia were not considered in this study, for example, concurrent usage immunosuppressant medications like cyclosporine, AZA or methotrexate (Béné et al., 2014). Furthermore, relying on FAERS database cannot provide us exact estimation of true volume of alopecia induced by a drug and there might be other factor that influences alopecia in psoriasis patients such as- genetic basis and environmental factors. Besides, in our study, we only analyzed the cases of psoriasis patients in general, and patients with psoriatic arthritis or plaque psoriasis were not individually determined. Hence, more research is needed to determine whether TNF-alpha inhibitors increase alopecia risk.

Chapter 6

Conclusion

To summarize, the mechanism by which TNF-α antagonists induce alopecia is not well understood. Disproportionality analysis was performed using the pharmacovigilance database to acquire signals for the generation of alopecia in psoriasis patients when treated with TNF-alpha inhibitors. The severity of the drugs of interest were also analyzed by comparing them with docetaxel, an alopecia-causing agent. These findings give important information when the administration of TNF-alpha inhibitors are considered for treating of patients with psoriasis. In our study, it has been identified that infliximab and certolizumab pegol show a significant signal for alopecia. On the other hand, golimumab, etanercept and adalimumab did not show any significant signal. Certolizumab pegol showed the greatest ROR among the other drugs evaluated and etanercept had the lowest. The results from our sensitivity analyses can be crucial for providing information about whether TNF-alpha inhibitors can be used for treatments. Sometimes the stimulated or nocebo reporting might lead to biasness of the results. So, there is a need for conducting cohort studies to validate the results from the analyses and confirm the safety of TNF-alpha inhibitors in psoriasis patients.

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