Drug Induced Nervous System Disorder Associated with HUMIRA in Treatment of Ankylosing Spondylitis: A Pharmacovigilance Study Based on FDA Adverse Event Reporting System (FAERS) Database

By

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project 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 project 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 "Drug Induced Nervous System Disorder Associated with HUMIRA: A Pharmacovigilance Study Based on FDA Adverse Event Reporting System (FAERS) Database" submitted by Asma Jashim (20146031), of Spring 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract

Ankylosing spondylitis is a genetically inherited rare autoimmune disease. This systemic, seronegative inflammatory spondyloarthropathy fuse and destroy the sacroiliac joints and spinal vertebrae. There are numerous therapeutic choices for this disease, such as TNF-α inhibitors, DMARDS, NSAIDS, and several more. This study's drug of choice is adalimumab, a completely human monoclonal antibody that is also used to treat ankylosing spondylitis and is marketed under the name HUMIRA. Adalimumab has several severe adverse effects, such as nervous system disorder, despite being effective in treating the symptoms of autoimmune diseases. In this study, post-market surveillance case reports from the FAERS database were used to investigate the connection between treatment with adalimumab and nervous system disorders based on age and gender. In addition, incidents reported by healthcare professionals were listed separately to reduce biases. The results were calculated using reporting odds ratio (ROR) and 95% CI to support or disprove the association.

Keywords: Ankylosing Spondylitis; ROR; Biologics; FAERS; Adalimumab; Nervous System Disorder

Dedication

Dedicated to my beloved mother, who constantly supported me throughout all ups and downs of my life.

Acknowledgement

First and foremost, I want to start by thanking Allah (SWT) for giving me patience and strength during the project.

I would like to express my gratitude to Tanisha Momtaz ma'am, my respected supervisor, for her invaluable counsel and support during this project amidst of her busy schedule. Without her encouragement and feedback, the project could not be finished. Additionally, I want to thank all of the School of Pharmacy's faculty members for their support, direction, and assistance during my undergraduate studies. Their excellent teaching approach and unwavering encouragement inspired me to acquire new knowledge all the time. I would especially like to thank Fardin Salekin Khan bhai, my esteemed senior and former teaching assistant at the School of Pharmacy, for teaching me data analysis for my thesis. Last but not least, I want to express my appreciation to my parents and friends for supporting and believing in me.

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List of Acronyms

AS	Ankylosing Spondylitis
TNF	Tumor Necrosis Factor
WHO	World Health Organization
HLA	Human Leukocyte Antigen
ERAP1	Endoplasmic reticulum aminopeptidase 1
NSAID	Non-Steroidal Anti-Inflammatory Drugs
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
DMARD	Disease-Modifying Antirheumatic Drugs
BASFI	Bath Ankylosing Spondylitis Functional Index
FDA	Food & Drug Administration
FAERS	FDA Adverse Event Reporting System
IL7	Interleukin 7
MMP3	Matrix Metallopeptidase 3
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
CYP450	Cytochrome 450
MedDRA	Medical Dictionary for Regulatory Activities

Chapter 1

Introduction

1.1 Ankylosing Spondylitis

Ankylosing spondylitis is a rare autoimmune disease which can be genetically inherited. It can affect 1% of the general population. This is a systemic, long-term, seronegative inflammatory spondyloarthropathy that fuse and destroy the sacroiliac joints and spinal vertebrae. This particular form of arthritis inflames the ankles, knees as well as hips, along with the joints and ligaments of the spine. Normally, the spine's ligaments and joints facilitate bending and movement. Ankylosing spondylitis can result in stiffness due to inflammation in the spine's joints and tissues, and in the worst cases, the vertebrae may fuse (N.S.C.A.O, 2024). Among the rheumatic diseases originally classified as the seronegative spondyloarthropathies, but now often known as spondyloarthritis (SpA), ankylosing spondylitis is an example of a broad range of arthritides. Apart from axial arthritis, it can also cause uveitis, enthesitis, and peripheral arthritis—all of which are common features of the SpA (John Hopkins Arthritis Center, 2019).

1.2 Symptoms

Ankylosing spondylitis symptoms typically appear gradually over a few months or years. Over many years, the symptoms can fluctuate and get better or worse. AS usually begins to emerge in people ranging in age from 18 to 40 (NHS, 2023). The initial signs and symptoms of nr-axSpA are frequently reported as lower back and buttocks pain and stiffness that lasts for a few weeks or months. Initially, pain may be experienced on one side exclusively or on alternate sides. Usually, the pain is not localized; instead, it is dull and diffuse. These symptoms can occasionally be rather bad. In nr-axSpA, a person's sex may have an impact on where their initial pain occurs. Men are more likely to experience symptoms in the lower back, but some

women get symptoms in the neck and other peripheral joints first (Medications Used to Treat Ankylosing Spondylitis and Related Diseases, n.d.). Main symptoms include:

- **Back pain and stiffness:** This is the most prevalent symptom of ankylosing spondylitis. Depending on the time of day, the condition becomes worse in the morning and at night, may get better with exercise but gets worse with rest.
- **Arthritis**: Patients with this condition experience pain when moving the affected joint. Along with swelling, warmth is felt in the affected area.
- **Enthesitis:** A painful inflammation develops where a ligament or tendon attaches to a bone.
- **Fatigue:** Tiredness and lack in energy.
- **Iritis:** Alternatively called acute anterior uveitis, where redness and swelling occur in the anterior segment of the eye. In extreme cases, it can result in blindness in addition to light sensitivity and impaired vision.
- **Psoriasis:** A skin disorder emerged as a result of an immune system overreaction, which caused rapid multiplication of skin cells, resulting in flaky areas of skin that formed scales.
- **Inflammatory bowel disease (IBD):** Cause stomach pain and diarrhea.

1.3 Prevalence of Ankylosing Spondylitis

Researchers have yet to determine the specific cause of ankylosing spondylitis. Despite this, substantial research on the disease and its etiology has been undertaken during the previous decade. Nonetheless, an impact appears between the frequency of ankylosing spondylitis (AS) in a particular community and the existence of HLA-B27. According to research, each continent has a different prevalence of AS worldwide. After reviewing 36 pertinent papers, the

mean prevalence rates of ankylosing spondylitis were found to be as follows: In North America: 31.9 per 10,000; in Asia: 16.7 per 10,000; in Europe: 23.8 for every 10,000; 7.2 out of 10,000 in Africa and 10.2 out of 10,000 in Latin America. The survey estimates that European instances range from 1.30 million to 1.56 million as well as Asia has between 4.63 million and 4.98 million instances. The researchers discovered enough data to make these estimates. Researchers also looked at the global population with spondyloarthritis, a more general category of arthritis (Giorgi, 2023).

It was estimated that between 5% and 6% of people who tested positive for HLA-B27 suffer from AS. HLA-B27 prevalence varies among ethnic groups in the United States (Wenker & Quint, 2023). In the same research, a survey conducted in 2009 found rates of HLA-B27 prevalence among 4.6% of Mexican Americans. and Black non-Hispanic people at 1.1% and 7.5% of non-Hispanic White people (Wenker & Quint, 2023).

1.4 Association of HLA-B27 Gene with Ankylosing Spondylitis

HLA-B27, or human leukocyte antigen (HLA) class I molecule B27, has been shown to have a high correlation with the advancement of AS by limiting immune responses and triggering autophagy responses. In AS patients, more than 100 distinct different B27 alleles (HLA-B2701 to HLA-B27106) have been identified; B2705 and B2702 are particularly common in European ethnicities, while B2704 is more prevalent in Asian ones (Lin & Gong, 2017). On the other hand, B2709 and B2706 are not associated to any diseases. Most of these subtypes merely differ in a limited quantity of amino acids, that alter the molecule's peptide-binding capabilities. All populations contain HLA-B2705, which is thought to have been the "parent" or initial HLA-B27 molecule (Reveille, 2006). The mechanism linking HLA-B27 to ankylosing spondylitis remains unknown despite extensive research conducted since the disease's relationship with HLA-B27 was discovered in the early 1970s. Currently available theories fall

into two main categories: those that affirm HLA-B27's canonical functions in peptide presentation (the "arthritogenic peptide" theory) and those that discuss aberrant properties of HLA-B27 itself, like the propensity to form homodimers and/or the induction of stress in the endoplasmic reticulum as the consequence of developing HLA-B27 molecules folding slowly and inefficiently (Evans et al., 2011).

The notion of arthritogenic peptides states that AS is triggered by HLA-B27's tendency to bind to one or more antigenic peptides, either produced by the body or by bacteria. Following this binding, the peptide(s) triggers a cytotoxic T-cell response that is inhibited by HLA-B27. Such a peptide could be attached to and all disease-associated HLA-B27 subtypes exhibit this trait, although other HLA class I molecules do not. Nevertheless, as of yet, no such "arthritogenic peptide" has been discovered. (Reveille, 2006).

Another theory proposes that AS may result from HLA-B27 molecule misfolding. In vitro, homodimers containing HLA-B27 heavy chains that rely on disulphide binding due to their a1 domain cysteine-67 residues can be formed. B27 misfolds in the endoplasmic reticulum, resulting in these homodimers. An intracellular stress response that is pro-inflammatory, carried on by the buildup of misfolded protein may have an impact on the onset of SpA. As an alternative, once on the cell surface, it is possible for the B27 homodimers to bind to receptors on other inflammatory cells. or transform into antigenic compounds. It is unclear if the development of HLA-B27 homodimers is limited to SpA or even associated with its presence. (Reveille, 2006).

The correlation between ankylosing spondylitis and Endoplasmic Reticulum Aminopeptidase 1 (ERAP1) is restricted to those who are HLA-B27-positive, based on disease models that link improper peptide trimming or presentation by ERAP1 and HLA-B27 to the genesis of HLA-B27-associated disease. Another important source of information on potential disease

mechanisms in ankylosing spondylitis is the interaction between HLA-B27 and ERAP1 (Evans et al., 2011)

1.5 Treatment Strategies for AS

The primary objectives of AS treatment are to minimize side effects, enhance and maintain an ideal posture and spinal mobility, alleviate pain and lessen functional restrictions. The two foundations of drug therapy are TNF-α inhibitors (TNFis) and nonsteroidal anti-inflammatory drugs (NSAIDs). Other options for treatment include secukinumab, a non-TNFi biologic along with methotrexate and sulfasalazine. Two oral small-molecule Janus kinase inhibitor, tofacitinib and filgotinib, otherwise called JAK inhibitors that have been approved for AS, have demonstrated success in clinical trials (Zhu et al., 2019)

In the United States, tofacitinib (XELJANZ) is the first exclusive oral JAK inhibitor which granted approval for five distinct purposes. Adults suffering from severe Psoriatic arthritis (PsA), patients with active AS, active polyarticular course juvenile idiopathic arthritis in children beyond the age of two, adults suffering from moderately to highly active rheumatoid arthritis (RA) as well as adults who have mild to severe ulcerative colitis (UC) are advised to take it if they have not responded well to, or are intolerant of, one or more TNF blockers (Polyarticular course juvenile idiopathic arthritis-pcJIA) (Pfizer, 2021). Patients are typically offered secukinumab or ixekizumab if TNF-alpha inhibitors are not appropriate or do not sufficiently control the symptoms. As an alternative to secukinumab or ixekizumab, tofacitinib may not be as safe for certain individuals with ankylosing spondylitis, such as those who smoke or are over 65. Evidence from clinical trials indicates that tofacitinib outperformed a placebo in the treatment of active ankylosing spondylitis. Although tofacitinib and secukinumab or ixekizumab have not been directly compared, an indirect comparison of treatment outcomes indicates that Tofacitinib is equally effective (Mohanakrishnan et al., 2022).

1.5.1 Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are the first line drug therapy in the treatment of ankylosing spondylitis, which include those in the Coxib class. NSAIDs are an extensive class of drugs that are widely prescribed to relieve pain, decrease inflammation, and lower a high fever. Examples of NSAIDs include Naproxen, Etoricoxib, Diclofenac sodium, Ibuprofen, Celecoxib, Piroxicam, Meloxicam etc.

According to a recent study, the prostaglandin E receptor 4 (PTGER4) gene is correlated with ankylosing spondylitis. This receptor is associated with bone absorption. NSAIDs suppress the synthesis of prostaglandin, which thereby results in reduced absorption. Since each patient responds differently and has varying levels of therapeutic potency, selecting the best NSAID drug is challenging. The best way to deliver the medications has always been up for debate, but it is now widely agreed upon that they should be given continually (Moon & Kim, 2014). As a result of research showing that patients receiving medicine continuously had improved clinical results in terms of the progression of the disease (i.e., less new bone development) than those receiving medication only whenever they had pain. Other medications such as TNF-α inhibitors should be taken into consideration if the Bath ankylosing spondylitis disease activity index (BASDAI) is greater than 4 and if no improvement in symptoms is seen even after NSAID treatment (Moon & Kim, 2014).

1.5.2 Acetaminophen & Opioid Analgesics

When used in addition to other therapies, acetaminophen and tramadol showed promise in treating patients with ankylosing spondylitis. Combination acetaminophen/tramadol tablets function as pure analgesics rather than as anti-inflammatory drugs. Up until week 12, the add-on impact of the combination of tramadol/acetaminophen tablets showed a steadily rising advantage. The delayed action of tramadol and paracetamol combination tablets was likely caused by the central desensitization action of these drugs in pain pathophysiology, as

evidenced by the fact that they did not demonstrate a statistically significant effect for the short term until week 12 (Chang et al., 2013). Furthermore, while acetaminophen is not recommended for the treatment of ankylosing spondylitis, it might be taken into consideration in case other treatments fail to relieve the pain (Dewitt & Surgeon, 2018).

Opioids worsen patient outcomes for AS patients; they include depression, increased scores on the Bath Ankylosing Spondylitis Disease Activity Index, and a worse Bath Ankylosing Spondylitis Functional Index. Opioid use is linked to a higher rate of initial treatment failure with tumor necrosis factor inhibitors in AS patients. Therefore, the administration of opioids in treating rheumatic disease may result in an increased incidence of adverse events and a decrease in the efficacy of therapies targeted at the condition (Sheahan et al., 2024). Higher level of BASDAI and BASFI, increased duration of disease, depression, smoking, inactivity, radiographic severity, and cardiovascular disease were among the factors substantially linked to opioid usage, particularly chronic opioid use. Drugs including antidepressants, hypnotics, muscle relaxants and were more frequently used by patients on opioids. The link between smoking, aging, and Psychoactive drugs and subjective, but not objective, indicators of disease progression was highlighted by multivariable analysis (Dau et al., 2018).

1.5.3 Disease-Modifying Anti-Rheumatic Drug (DMARDs) Therapy

Although there is no data that supports their efficacy, disease-modifying antirheumatic drugs (DMARDs) are frequently used as second-line therapy for AS. The word "DMARD" was taken from rheumatoid arthritis, and no DMARD has been demonstrated to stop or considerably slow down the rate at which structural damage progresses—a prerequisite for being classified as an AS disease-controlling antirheumatic drug (Akkoc et al., 2006). Till date, DMARDs such as methotrexate and sulfasalazine do not appear to be effective in treating axial SpA symptoms in the neck and spine. Only patients with axial SpA who have peripheral disease should take

DMARDs, suggesting that DMARDs may be able to alleviate arm, ankle, hip, or knee pain (NSAIDs Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Reduce Pain and Inflammation, n.d.).

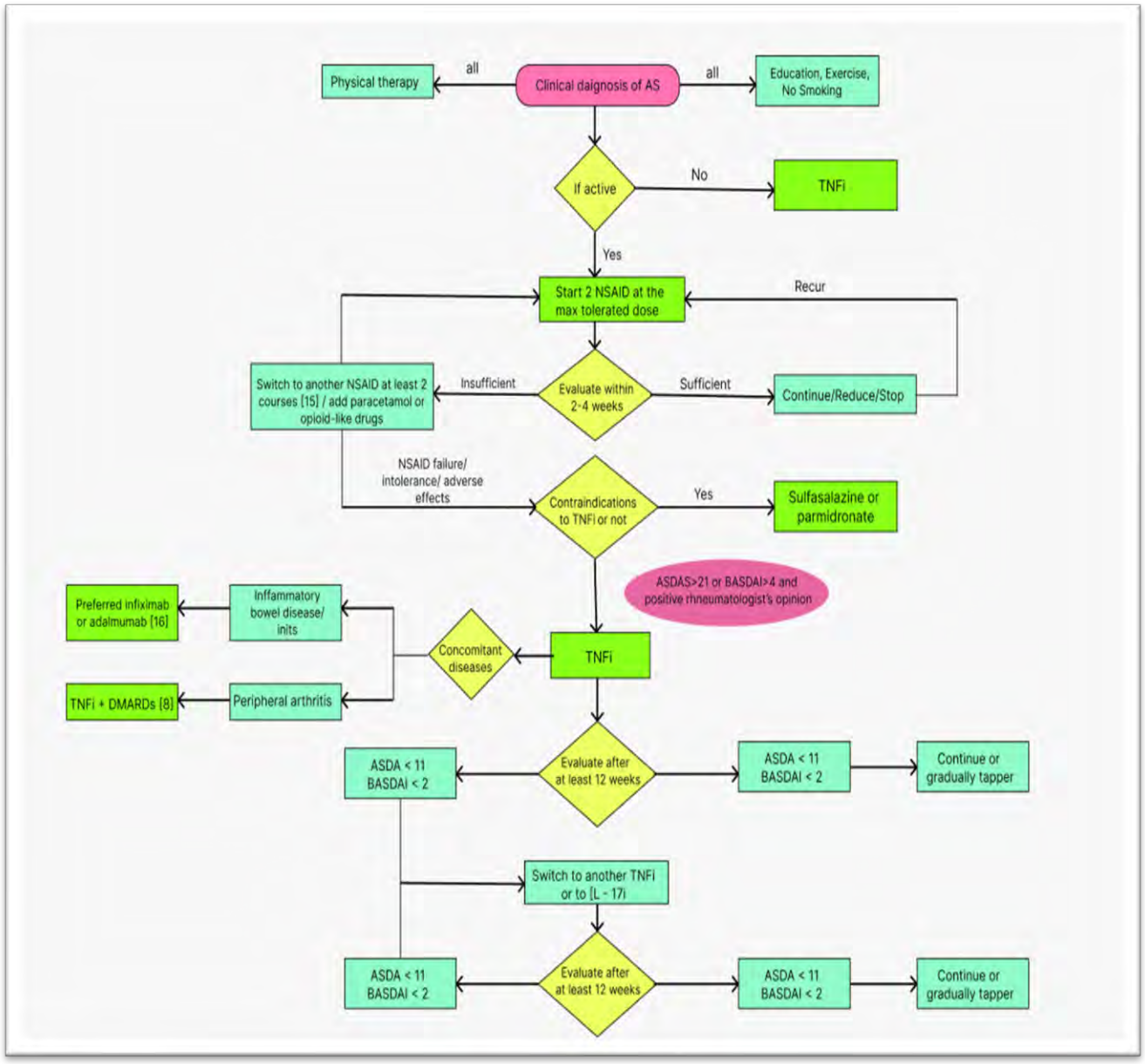

Figure 1: Drug treatment strategy for ankylosing spondylitis patients (modified from: (Zhu et al., 2019)

1.5.3.1 Sulfasalazine

Sulfasalazine is useful in the early diagnosis of pediatric patients because it can restrict leukocyte migration, lower the activity of proteolytic enzymes, and block the effects of certain cytokines. However, according to a recent suggestion, this dug should only be used for patients with persistent peripheral arthritis who are unable to take TNF inhibitors due to side effects or other factors (Wang et al., 2020).

1.5.3.2 Methotrexate

Methotrexate is a type of immunosuppressant that reduces inflammation and slows down the immune system. It is an antagonist of folic acid that inhibits DNA synthesis and hence suppresses the function of certain cytokines (Wang et al., 2020). This chemotherapy drug was initially developed to treat cancer, but it is now often used and frequently highly effective in treating rheumatoid arthritis. It is usually not used for treating spinal arthritis and is prescribed in smaller doses to alleviate spondyloarthritis symptoms (Overview of Non-Radiographic Axial Spondyloarthritis (Nr-AxSpA), n.d.). Methotrexate is available as an oral tablet or as a self-injectable dose in a prefilled injection pen. It is also required to take vitamin folic acid when taking methotrexate to help suppress potential adverse effects, such as nausea and oral ulcers. Liver function and blood counts must be monitored often due to additional potentially dangerous side effects. Due to its history of birth abnormalities and fetal fatalities, methotrexate is highly contraindicated in pregnant women (Overview of Non-Radiographic Axial Spondyloarthritis (Nr-AxSpA), n.d.).

1.5.4 Corticosteroids

Drugs called glucocorticoids, sometimes referred to as corticosteroids or simply steroids, are used to treat inflammation. Oral glucocorticoids such as prednisone and methylprednisolone are most frequently administered. The doctor may also directly inject corticosteroids into the

affected joint(s). The action of glucocorticoids is similar to that of hormones, or natural steroids, produced by the kidney's adrenal glands. They have the ability to reduce inflammation and lower immune system activity (Creakyjoints, n.d.). It is common, though sometimes controversial, to use corticosteroids to treat arthritis pain. However, long-term side effects from corticosteroids include immunosuppression, an increased risk of infections, ulcers, and osteoporosis, to name a few (Hunter et al., 2021).

1.5.5 TNF-α inhibitors

TNF-α, a cytokine, exhibits pleiotropic effects on several cell types. It has proven to be a significant regulator of inflammatory responses and it's indicated in the aetiology of several autoimmune and inflammatory diseases. TNF-α is a homotrimer protein of 157 amino acids that is primarily produced by activated macrophages, T lymphocytes, and natural killer cells. TNF-α is found in both soluble and transmembrane forms (Jang et al., 2021).

The TNF-converting enzyme converts the precursor TNF into soluble TNF undergoing proteolysis which then becomes the physiologically active homotrimer TNF after oligomerization. TNF has two distinctive yet closely related forms: TNF-alpha and TNF-beta. Except for erythrocytes, almost all cell types have TNF receptors I and II (TNFRI and TNFRII), which are the binding sites for both TNFs (Gerriets et al., 2023).

TNF-α is physiologically essential for a healthy immune response. Although TNF-α can help control the immune system, producing excessive or insufficient amounts can be hazardous and even cause disease. TNFα inhibitors have proven effective in treating autoimmune illnesses in clinical settings, perhaps due to TNF-α's role in developing these conditions. Therapeutic medications function as antagonists by preventing TNF-α from interacting with TNFR1/2, or as agonists in certain circumstances by inducing reverse signaling and triggering the death of immune cells that produce TNF-α (Jang et al., 2021).

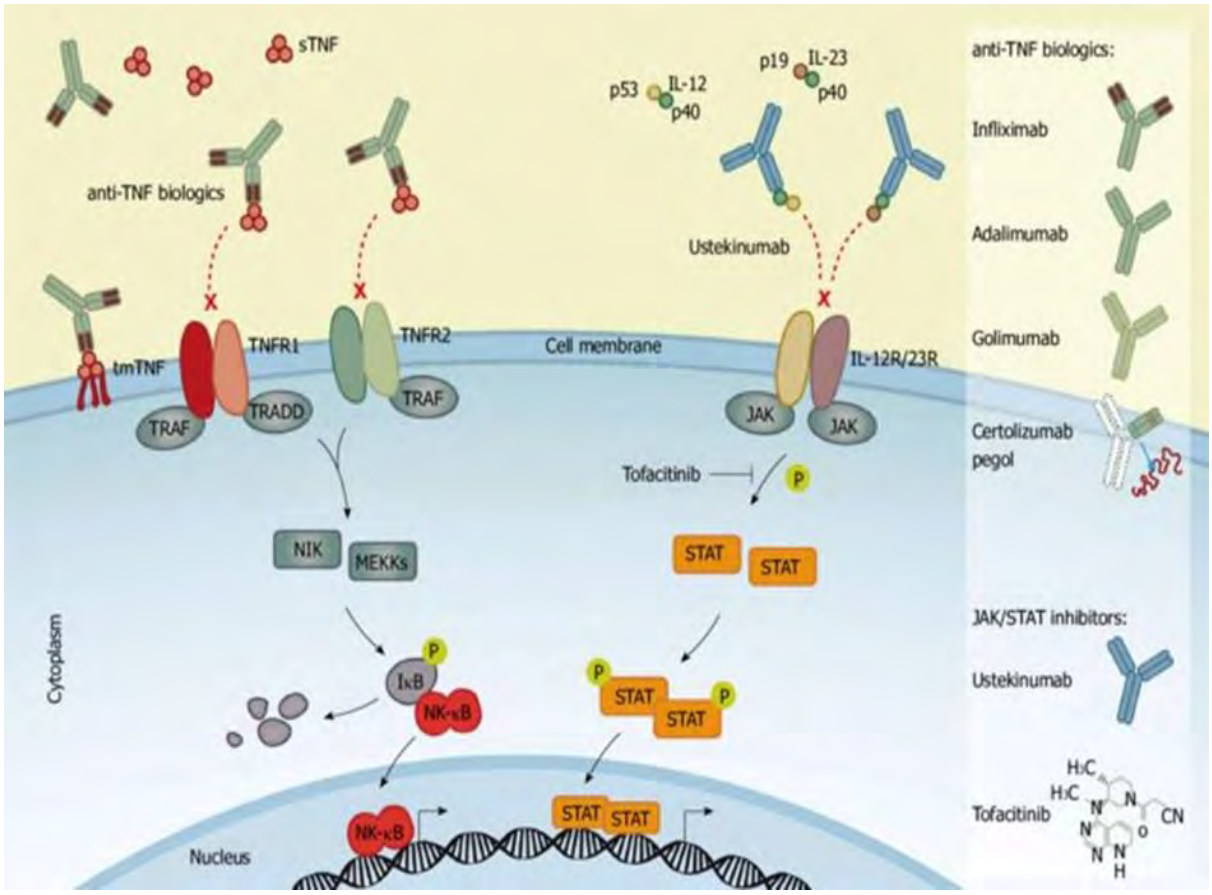

Figure 2: The mechanism of action of Janus kinase/signal transducer and activator of transcription signalling inhibitors and anti-tumour necrosis factor biologics (modified from: (Pedersen et al., 2014)

On the left panel of the figure, tumour necrosis factor (TNF) biologics inhibits TNF-α-mediated pro-inflammatory signalling through their binding to homotrimeric TNF-α [transmembrane (tmTNF-α) and soluble (sTNF-Ά)]. TNFR1 and TNFR2, the two TNF-α receptor types, are hence incompatible with the cytokine. As an example of an anti-TNF biologic, four drugs labelled for inflammatory bowel disease are provided: adalimumab and golimumab (completely human antibodies), certolizumab pegol (a pegylated Fab fragment of a humanised anti-TNF antibody), and infliximab (a chimeric antibody) (Pedersen et al., 2014).

Chapter 2

Adalimumab

2.1 Overview

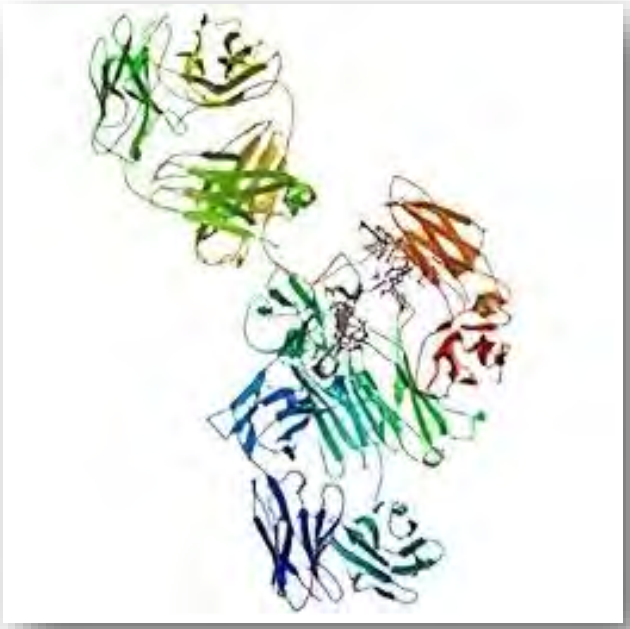

Figure 3: Protein structure of adalimumab (modified from (DRUGBANK Online, n.d.)

Adalimumab, a recombinant monoclonal antibody with higher affinity, was the third TNF-α inhibitor. A number of autoimmune conditions, such as ulcerative colitis, rheumatoid arthritis, psoriasis, as well as psoriatic arthritis, can be treated with adalimumab (Ellis & Azmat, 2023). Abbvie introduced it in the United States, and the FDA approved it in 2002. This drug is marketed by the name Humira. Using a mammalian cell expression system, recombinant DNA technology is used to develop it. For subcutaneous self-administered doses, the drug is available in convenient pen form and prefilled syringe form (DRUGBANK Online, n.d.).

Pharmacodynamics: A number of indicators are reduced by adalimumab, including interleukin 6 (IL6), interleukin 7 (IL7), matrix metalloproteases, soluble intercellular adhesion

molecule 1 (ICAM1), matrix metallopeptidase 1 (MMP1), matrix metallopeptidase 3 (MMP3) and C reactive protein (CRP). Furthermore, Adalimumab alters the expression of adhesion molecules, consisting of selectin E (SELE), intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) (PHARMGKB, n.d.). Adalimumab-treated rheumatoid arthritis patients showed decreased baseline values of inflammatory acute phase reactant proteins c reactive protein [CRP] serum cytokines (IL-6) and erythrocyte sedimentation rate [ESR]) and There was additional evidence that the CRP levels of those with Crohn's disease were lower. Following adalimumab treatment, it was also shown that serum levels of matrix metalloproteinases (MMP-1 and MMP-3), which cause tissue remodelling and cartilage breakdown, were reduced. Many inflammatory disorders have been demonstrated to improve physical function, decrease disease signs and symptoms, induce a therapeutic response, and limit structural damage in both adult and pediatric patients (DRUGBANK Online, n.d.).

2.2 Mechanism of Action

Adalimumab’s molecular weight is around 148 kDa and is made up of 1330 amino acids. Adalimumab's mechanism of action by inhibiting TNF-α from attaching to its receptor and influences both the soluble and membrane-bound variations of the protein. Adalimumab selectively inhibits TNF-α's ability to connect with the cell surface TNF receptors, p55 (TNFR1) and p75 (TNFR2), thereby inhibiting cytokine-induced inflammatory processes. The reason for Adalimumab's excellent specificity for TNF-α and limited immunogenic potential is that it shares structural and functional characteristics with human IgG1 that occurs naturally. Adalimumab does not bind to or have any effect on lymphotoxin or interleukins, among other cytokines.

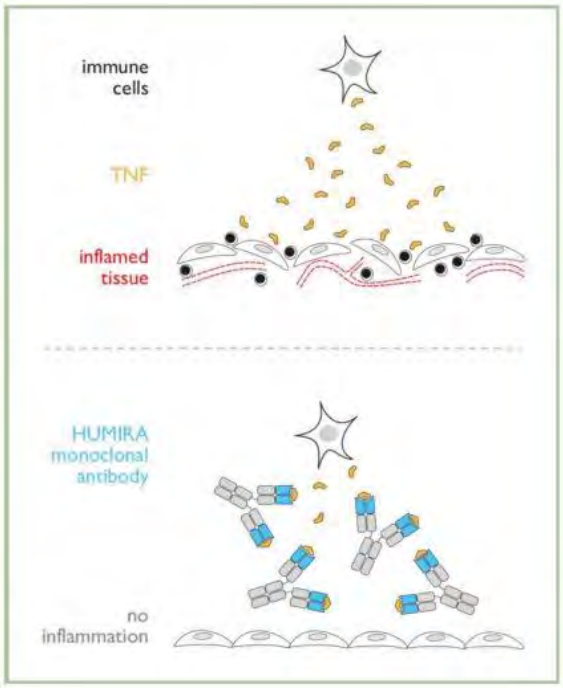

Figure 4: How Humira (Adalimumab) works (modified from: MRC Laboratory of Molecular Biology, 2023)

Adalimumab exhibits significant osteogenic properties. and because of that, it has higher efficacy in treating various kinds of arthritis. TNF activates the NF-κB and RANKL receptors on stromal or osteoblast cells. Its suppression thereby prevents the eventual deterioration of bone and cartilage. It also influences the growth and activation of osteoclasts, which is regulated by TNF blocking. Furthermore, anti-TNF drugs suppress serum matrix metalloproteinases 1 and 3. This broad effect led to TNF inhibitors' efficacy in arthritis treatment (Ellis & Azmat, 2023).

2.3 Pharmacokinetics

Table 1: Pharmacokinetic properties of adalimumab (derived from: (DRUGBANK Online, n.d.)

Absorption	After the administration of 40 mg of adalimumab on subcutaneous route to one healthy adult subject, the maximum serum concentration (Cmax) and the time to achieve the maximum concentration (Tmax) were noted to be 4.7 ± 1.6 µg/mL and 131 ± 56 hours. Following a single 40 mg subcutaneous dose of adalimumab, the average absolute bioavailability of adalimumab was determined from three clinical studies to be 64%. After a single intravenous injection, the pharmacokinetics of adalimumab demonstrated a linear pattern spanning the dose range of 0.5 to 10.0 mg/kg.
Volume of Distribution	Patients who suffer from rheumatoid arthritis receiving intravenous dosages ranging from 0.25 to 10 mg/kg noted a distribution volume (Vss) of 4.7 and 6.0 L.
Metabolism	Therapeutic mAbs are often metabolized in ways that do not include cytochrome P450-mediated pathways or interactions with cell membrane transporters (Ellis & Azmat, 2023).
Half-life	The terminal half-life varied between 10 and 20 days in each study, with an average of about 2 weeks.
Clearance	Adalimumab's single-dose pharmacokinetics in RA patients were established by multiple studies using intravenous doses ranging from 0.25 to 10 mg/kg. Adalimumab's systemic clearance is roughly 12 mL/hr. No evidence of changes in RA patients' clearance over time was found in long-term studies with dosing longer than two years.
Route of elimination	Adalimumab is most likely eliminated by the reticuloendothelial system through opsonization.

2.4 Drug-Drug Interaction

- Since adalimumab conjunction with anakinra or abatacept increases the risk of serious infections, medical authorities advise against doing so. Moreover, there was an increased incidence of severe infections in rheumatoid arthritis patients treated with rituximab and subsequently treated with TNF-α inhibitor blockers. It is not advised to provide adalimumab with other biologics, such as DMARDs or other TNF-α inhibitors, simultaneously due to the probability of higher risk of infection.
- Current results do not indicate that dosage modifications for either drug are required in patients receiving adalimumab in conjunction with methotrexate, even though methotrexate lowers the apparent clearance of adalimumab.
- During prolonged inflammation, elevated cytokine concentrations can inhibit the synthesis of CYP450 enzymes. Consequently, a drug that inhibits cytokine activity, such as adalimumab, may have an effect on the synthesis of CYP450 enzymes. Therapeutic drug monitoring (TDM) should be taken into consideration when starting or stopping adalimumab in patients receiving treatment with CYP450 substrates that have a narrow therapeutic index in order to assess the effect on drug concentration.
- Adalimumab should not be administered along with live vaccinations (Ellis & Azmat, 2023).

Contraindication: Adalimumab is highly contradicted with upadacitinib because the increase the immunosuppressive effect of each other and thereby cause infection (Cyltezo (Adalimumab-Adbm) Hadlima (Adalimumab-Bwwd) Hulio (Adalimumab-Fkjp) Hyrimoz (Adalimumab-Adaz) Idacio (Adalimumab-Aacf) Simlandi (Adalimumab-Ryvk) Yuflyma (Adalimumab-Aaty) Yusimry (Adalimumab-Aqvh) Rheumatoid Arthritis, n.d.).

Chapter 3

Methodology

3.1 Data Source

All the data used in this pharmacovigilance study were obtained from FAERS database. It is the Adverse Event Reporting System of FDA which is used for post market drug safety monitoring. Healthcare professionals and patients voluntarily notify pharmaceutical manufacturers or the FDA directly about adverse events that transpire during clinical practice. These case reports are submitted and enlisted to the FDA's Adverse Event Reporting System (AERS), which is an electronic safety database that includes cases that are reported on their own initiative. AERS is a computerized database that was started almost for 40 years ago and has over 3 million case reports in it. The FDA obtains reasonably priced safety data from spontaneously reported instances that are kept in the AERS database, enabling the identification of occurrences not observed in clinical studies. As a tool for identifying and investigating drug safety issues, AERS has significant limitations because it only includes case reports that were submitted on their own. Because multiple people may record the same occurrence, duplicate reports are included in the database (Weaver et al., 2008). Physicians, other healthcare providers, patients, and pharmaceutical corporations are among the many sources of these reports. Patient demographics, medication dosage, reported reactions, and terminology classified by the Medical Dictionary for Regulatory Activities (MedRA) are among the data that have been abstracted (Nguyen et al., 2021). Using sites like PubMed, ResearchGate, Google Scholar, the literature search was conducted.

3.2 Inclusion and Exclusion Criteria

The data reported from January 2019- December 2023 in the FAERS database were extracted and analyzed for this study. All the adult patients who voluntarily reported experiencing any

adverse event in FAERS while taking adalimumab, regardless of the indication or dosage, were included in this study. In order to ensure that any bias in the adalimumab reports, such as misclassification, was comparable to bias in the remaining data base, which served as the comparator, no patients were removed from the analysis, with the exception of duplicate reports. The case numbers, sex and event date eliminated redundant reports. The preferred terms (PTs) from MedRA that were used exclusively to search for case reports of nervous system disorders associated with adalimumab were "nervous system disorder" and "adalimumab."

3.3 Statistical Analysis

A disproportionality analysis was conducted by calculating the reporting odds ratio (ROR) and 95% confidence interval (CI). The confidence interval is calculated to assess how significant this result is. It provides an approximate range that the population will fall inside given the true odds ratio (Tenny & Hoffman, 2022). The calculated odds ratio will not be considered statistically significant if the odds ratio's confidence interval included the number 1. This is evident from how the odds ratio is interpreted. The exposed group has a higher probability of the event happening if their odds ratio is larger than that of the non-exposed group. If the odds ratio is less than one, this implies that the exposed group has a lower probability of experiencing the occurrence than the non-exposed group. If the odds ratio is precisely 1, it indicates that the exposed and non-exposed groups have equal chances of the event occurring (Tenny & Hoffman, 2022). All the statistical analysis were done with precaution to determine a precise result.

Chapter 4

Result

The reporting odds ratio (ROR) and 95% confidence interval have been calculated by analyzing the data gathered from the FAERS database. Though it appears similar to the case-control technique, this group of patients is referred to as "non-cases" rather than "controls" since they have all been exposed to at least one drug and have all had at least one reaction that isn't the adverse reaction of interest (Faillie, 2019).

Table 2: Results for cases of nervous system disorder using adalimumab

FAERS database values from 2019-2023				
	No. of cases	**ROR (Reporting odds ratio)**	**95% CI (Confidence interval)**	**P value**
Nervous system disorder	351	2.82	2.92 to 2.71	<0.001

Table 3: Results for cases reported by healthcare professionals

FAERS database values from 2019-2023				
	No. of cases	**ROR (Reporting odds ratio)**	**95% CI (Confidence interval)**	**P value**
Nervous system disorder	111	2.90	3.08 to 2.71	<0.001

Table 2 presents 351 cases of nervous system disorders caused by adalimumab, including both genders and regardless of the person who reported the case. The ROR (95% CI) was 2.82 (2.92-2.71; $p < 0.0001$). Healthcare professionals, including doctors, nurses, and pharmacists, reported 111 cases of nervous system disorders, which can be seen in the following table (Table 3). The ROR (95% CI) in this instance was calculated to be 2.90 (3.08 to 2.71; $p < 0.0001$).

Table 4: Results for cases of nervous system disorder using adalimumab based on gender

FAERS database values from 2019-2023				
Gender	**No. of cases**	**ROR (Reporting odds ratio)**	**95% CI (Confidence interval)**	**P value**
Male	103	2.57	2.76 to 2.37	<0.001
Female	222	2.99	3.12 to 2.85	<0.001

Table 5: Results for cases of nervous system disorder using adalimumab on most vulnerable age group (Over 65 years)

FAERS database values from 2019-2023				
	No. of cases	**ROR (Reporting odds ratio)**	**95% CI (Confidence interval)**	**P value**
Nervous system disorder	42	3.08	3.38 to 2.77	< 0.001

Furthermore, the ADR cases of interest based on gender and the most vulnerable age group are shown in the remaining two tables. 103 cases were reported for male whereas the number of cases reported for female was 222. 42 cases were listed for the most vulnerable age group which is over 65 years old. The ROR value of male cases was 2.57(2.76 to 2.37; $p < 0.0001$) and for female it was 2.99(3.12 to 2.85; $p < 0.0001$). For the cases reported for patients >65 years old, the ROR value was 3.08(3.38 to 2.77; $p < 0.0001$).

Chapter 5

Discussion

The ROR were calculated using the contingency table of the drug and number of adverse events. As discussed before, if the lower bound of 95% CI is greater than 1, it means the presence of a significant disproportionality signal. This indication of disproportionality signal can be explained as the drug of interest experiencing noticeably more adverse events than would be predicted by chance alone (Nguyen et al., 2021)

According to the results obtained from the FAERS database Reporting Odds Ratio values, adalimumab has significant effects on nervous system disorders. Because as per the calculation in table 2, the lower bound of 95% CI is 2.71 which is greater than 1.00. For the rest of the tables 3, 4 and 5, the 95% CI are also greater than 1, indicating the significant effect of adalimumab. It is evident from Tables 4 and 5 that nervous system disorders linked to adalimumab treatment are more prevalent in women and elderly people. According to a report published by World Health Organization, men experience greater disability and health loss from neurological disorders than women do, yet there are some conditions, such as dementia or migraines, where women are disproportionately affected (*Over 1 in 3 People Affected by Neurological Conditions, the Leading Cause of Illness and Disability Worldwide*, 2024). However, women continue to face gender prejudice in this diagnosis because males continue to be the preferred research subject in neuroscience despite all these significant sex differences. Among all the biologics and TNF-α inhibitors, adalimumab has been reported to have the highest number of nervous system disorder cases. It is also prominent in elderly people. Humans' innate immunity begins to deteriorate with age as physiological aging starts after 60 years of age. A deterioration in cognitive and motor abilities is closely linked to ageing. The primary alterations in the function of central cholinergic neurons includes decreased

acetylcholine synthesis and release, lower cholinergic receptor levels along with a considerable decrease in the number of muscarinic cholinergic neurons. The mechanisms behind the onset of neurological disorders in older people remain poorly understood. The processes governing cell death in the ageing brain remain unknown. It is unknown what circumstances make an older person more susceptible to neurological illnesses, as well as whether the ageing process triggers apoptosis and other mechanisms of neuronal death (Kowalska et al., 2017). The conclusion drawn from Table 5 supports the idea that an immunosuppressant such as adalimumab will significantly impact nervous system disorders and further reduce immunity in elderly people.

Table 4 indicates the bias associated with the adverse event reporting system. A total of 351 cases were reported from which only 111 cases were reported by healthcare professionals like physicians, nurses and pharmacists. The patients who were directly impacted or those who were associated with the patients reported the remaining cases. People lacking sufficient knowledge in healthcare may not always comprehend the negative consequences. Anyone can report any adverse effects they or their related ones have experienced because the FDA's adverse event reporting system is open to the public. Thus, there is a strong bias in such instances due to the cases that healthcare providers did not report. To reduce the bias, the cases were listed separately.

Chapter 6

Conclusion

The first monoclonal antibody to be developed, adalimumab, functions as a potent TNF-α inhibitor and is used to treat various autoimmune diseases. Any drug, nevertheless, might have side effects; these are especially common with disorders of the neurological system. This study's lack of information and research limitations prevent it from drawing a precise conclusion. The results from the FAERS database may be contested with further investigation because there is currently insufficient evidence on this adverse effect. As therefore, people should be made aware of this adverse effect, and in-depth study should be conducted while considering the medical history of the patient and carefully evaluating the accuracy of any reported cases.

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