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THE ROLE OF ADALIMUMAB IN UVEITIS PATIENTS

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ABSTRACT

The progress of multiple inflammatory cases in ophthalmology setting is wide spreading. Among which is Uveitis. It refers to a condition or ailment that involves the inflammation of the eye's middle layer referred to as Uvea. Its irritation or swelling is what is referred to as Uveitis. In this paper, I am reviewing published articles or researches using Adalimumab in the treatment of uveitis patients. Pubmed search was conduct. Sources are limited due to lack of publications in the unique and rare condition.

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INTRODUCTION

Health is one of the most crucial aspects of any human beings. It goes without saying that it is one of the things on which many people and governments spend quite a large amount of their income or revenue. This may be because of its bearing on the overall economic development and progress of an individual and the entire nation, as well. Nevertheless, recent times have seen an increase in the number and magnitude of ailments that affect the health of human beings. Of course, tremendous research has continuously been done in an effort to eliminate the prevalence of these ailments and safeguard the health of individuals. One of the ailments for whose intensive research has been done is Uveitis. Uveitis refers to a condition or ailment that involves the inflammation of the eye's middle layer referred to as Uvea. Uvea is responsible for the provision of the larger part of blood supply to the eye. Its irritation or swelling is what is referred to as Uveitis. This condition may result from autoimmune disorders such as exposure to toxins, infection, ankylosing spondylitis or rheumatoid arthritis (Schmitt and Wozel, 2009).

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In most cases, however, the cause of this condition is unknown. There exist varied forms of Uveitis.

- Anterior Uveitis is the most common type ad involves the inflammation of the front part of the human eye. It is commonly referred to as Iritis since it mostly affects the colored part of the eye referred to as the Iris. As much as this inflammation is mostly associated with autoimmune ailments, quite a large number of cases involve healthy people. It may affect a single eye only and is common in middle-aged, as well as young people (Schmitt and Wozel, 2009).
- Posterior Uveitis is an inflammation that mainly affects Uvea's back part, and mainly involves the choroid, which is a layer of blood vessels, as well as connective tissue situated in the middle part of the eye. Posterior Uveitis is also called choroiditis, but may also be called chorioretinitis in cases where it affects the retina. An individual is predisposed to this condition in cases where he has a systemic (body-wide) infection or an autoimmune disease (Wiens *et al*., 2010).
- Pars Planitis is an inflammation that affects pars plana, the narrowed area between the choroid and the iris. It is mainly common in young men and is not associated with other ailments. Some evidence suggests, however, that it may be

associated with multiple sclerosis and Crohn's disease (Wiens *et al*., 2010).

Uveitis, like other ailments, needs to be subjected to prompt diagnosis and treatment, otherwise serious complications such as permanent loss of vision, glaucoma and cataracts may result in cases where it is untreated (Schmitt and Wozel, 2009). The high co-occurrence of Juvenile Idiopathic arthritis (JIA) and Uveitis has raised concerns about the eye health of young people, not to mention their joints since the presence of the two diseases has a bearing on the choice of drug and pharmacotherapy. Statistics from the American Uveitis Society (AUS) indicate that approximately 6% of Uveitis cases occur in children. Up to 80% of the cases, however, are associated related to JIA. This makes the ailment the most commonly identified predisposing factor or cause of Uveitis in kids. A larger percentage of children who have JIA and Uveitis are either unresponsive to treatment (25%) or are suffering from a severe category of the ailment. Overall, a total of 75% of children suffering from Uveitis undergo visual loss as a result of varied eye complications. Up to 12 percent of people with Uveitis resulting from JIA develop an irreversible loss of vision, thanks to the chronic low-grade inflammation of the eye. One of the most crucial factors in the pathogenesis of Uveitis is TNF-a, the cytokine Tumor Necrosis Factor alpha. In animal experiments, this factor has often been detected. High levels or levels of inflammatory cytokines like TNF-a are implicated or blamed in the determination of causes of Uveitis. The cytokines are known to induce the expression of adhesion molecules and chemokines, as well as other cytokines that are known to prolong inflammation.

Therapy

The initial line of basic therapy for Uveitis involves topical and systemic corticosteroids, which are usually reinforced by methotrexate. Methotrexate acts as a second-line Disease-Modifying Anti-Rheumatic Drug (DMARD). As noted earlier, TNF-a or Tumor Necrosis Factor-alpha plays a crucial role in the growth and development of Uveitis. In essence, Tumor Necrosis Factor-alpha blockers have often been used in the treatment of Juvenile Idiopathic Arthritis and Uveitis. This is especially in the case of Uveitis that associated with Juvenile Idiopathic Arthritis in patients who have the traditional topical, as well as second-line DMARD therapy.

Rationale for the use of TNF-a inhibitors

The inhibition of TNF-a activity prevents the destruction of tissues in EAU, leads to the suppression of the Th1 effector mechanism and suppresses the activation of the infiltrating macrophages (De Vos *et al*., 1995). Anti-TNF therapy has also proved to be effective in altering peripheral blood T cells in individuals suffering from posterior segment intraocular inflammation. This contributes immensely to the recovery of their visual function. TNF-a levels, in patients suffering from Uveitis, are raised in the aqueous humour and serum. In essence, the inhibition of TNF-a activity may be effective in treating Uveitis, thanks to its pivotal role in the inflammation (De Vos *et al*., 1995). This has triggered the development of varied anti-TNF-a therapies, which were originally established for combating rheumatoid arthritis. Numerous anti-TNF therapies have been developed such as infliximab and etanercept. Recent times have also seen the development of another anti-TNF-a therapy known as adalimumab.

Adalimumab

Adalimumab refers to a recombinant human IgG1 monoclonal antibody known to act through inhibiting the activity of Tumor Necrosis Factor Alpha (TNF-a). As noted earlier, TNF-a is an inflammatory protein that triggers inflammatory responses of certain autoimmune diseases, especially in cases where it is produced in excess (Yue *et al*., 2009). Adalimumab tightly binds or adheres to the human TNF-a with a highly explicit affinity, thereby providing a block by interacting with the p75, as well as p55 cell-surface TNF receptors. In addition, adalimumab may, in the presence of a complement, lyse the surface TNF-expressing cells in vitro (Yue, *et al*., 2009). It is worth noting that inflammation is a reaction of the body to an injury and is necessary for the repair of such injuries. Adalimumab is a manmade or synthetic antibody that is known to bind or adhere to TNF in one's body, thereby blocking the effects of the alpha factor. This results in a reduction of inflammation, as well as the resultant consequences (Mushtaq *et al*., 2007). Adalimumab prevents or slows down the progressive destruction of joints in arthritis and is, therefore, a disease modifying antirheumatic drug (DMARD). Adalimumab is the first fully human anti-TNF-a monoclonal antibody that comes with a structure and function that cannot be distinguished from the human IgG1, as well as a similar half-life of approximately 2 weeks (Dick *et al*., 1998). It has been endorsed for the treatment of psoriatic arthritis, rheumatoid arthritis, psoriasis, ankylosing spondylitis, inflammatory bowel disease, as well as juvenile chronic arthritis. It may be used alone or combines with other DMARD such as methotrexate (Mushtaq, *et al*., 2007). It is noteworthy, however, that as much as much as the drug is highly specific it does not inhibit lymphotoxin called TNF-b. TNF-b is a cytokine that is produced by lymphocytes and affects varied cells (Rudwaleit, *et al*., 2009). It also modulates a number of biological responses resulting from TNF-a stimulation. These biological responses are known to have a significant influence on three adhesion molecules that cause leukocyte migration. These are intercellular adhesion molecule, endothelial leukocyte adhesion molecule and vascular cell adhesion molecule (Rudwaleit *et al*., 2009).

Dosage

Adalimumab is administered through a subcutaneous injection. Adult patients have 40 mg of the drug administered once every week (van de Putte *et al*., 2004).

Studies and statistics on the use of adalimumab

Numerous studies have been carried out on the effectiveness of adalimumab in treating ocular inflammation. A study carried out in Columbia showed high effectiveness of the drug with 13 out of 14 children responding to it (van de Putte *et al*., 2004). In a study done in 2008, adalimumab proved to be an appropriate and valuable option for treating Uveitis associated with refractory juvenile idiopathic arthritis. 15 out of 54 patients diagnosed with Uveitis showed improved disease

activity after adalimumab therapy while 7 patients experienced a worse disease activity (Nestorov, 2005). Altogether, there was an improvement in the ailment for 31 out of the 54 patients involved in the experiment as 16 more patients suffering from Uveitis had a moderate response to the drug, but never reached two-fold change (Nestorov, 2005). No change, however, was seen in 16 patients. It is worth noting that clinical evaluation has shown better results than this, as far as the use of adalimumab is concerned. Adalimumab has shown superior results to those of earlier therapies because it adheres to the TNF-a on the cell surface rather than just in the circulation. Moreover, biweekly or weekly administration is seen to have a more consistent serum level than intermittent infusions of other medications such as infliximab (National Institute for Health and Clinical Excellence, 2010). A decrease in ocular inflammation was noted in most patients, with a sustained response to the therapy after an average of 18months and a decrease or complete discontinuation of dosage of other immunosuppressive agents. The patients used in this case had responded poorly to conventional therapies for Uveitis (National Institute for Health and Clinical Excellence, 2010). In addition, the use of adalimumab has been approved by the FDA in reducing symptoms and signs of active arthritis in patients suffering from psoriatic arthritis. In this case, adalimumab may be used alone or combined with DMARDs or methotrexate (Rudwaleit *et al*., 2009). This approval was based on two controlled clinical studies that evaluated the efficacy or effectiveness and safety of the drug, whose results were compared with the use of non-steroidal anti-inflammatory drugs on psoriatic arthritis. It is worth noting that arthritis has been seen as one of the key risk factors for Uveitis (Rudwaleit *et al*., 2009).

Drug interactions

As much as the effectiveness of this drug has been proven in treating Uveitis, Methotrexate may reduce its absorption by 29 to 49 percent. Nevertheless, it is not necessary to make any adjustments to the dosage of adalimumab in cases where methotrexate is administered concomitantly (National Horizon Scanning Centre 98). However, there are instances where the severe infections result from combining the drug with other medications such as Kineret (anakinra). It is worth noting that adalimumab may limit the effectiveness of vaccines. In essence, it is imperative that live vaccines and attenuated vaccines are not administered while the patient is undergoing adalimumab therapy (National Horizon Scanning Centre, 2007).

Side effects of adalimumab

Adalimumab comes with a number of side effects that have varying levels of severity. Some of the most common or prevalent side effects include redness, swelling, as well as itching and pain at the injection site (Tynjala *et al*., 2008). Moreover, adalimumab is known to suppress the immune system, in which case it is associated with a number of minor infections affecting the sinuses, respiratory tract and urinary tract. Adalimumab, like other TNF inhibitors, is also associated with severe infections such as fungal infections, tuberculosis and sepsis (bacteria in the blood). It is imperative that adalimumab is not used on individuals who have active infections (Tynjala *et al*., 2008). In addition, adalimumab may worsen the signs of diseases affecting the nervous system. Studies have shown that some patients who use TNF inhibitors such as adalimumab have developed cancer. However, the connection between the use of adalimumab and development of cancer is unclear since individuals suffering from rheumatoid arthritis stand a higher chance of contracting cancers than the general population (Mansour, 2004). Other adalimumab side effects may include reduced levels of red cells and platelets in the blood (aplastic anemia) and hypersensitivity reactions such as anaphylaxis. The drug is also known to heighten the risk of reactivating the hepatitis B virus especially where chronic carriers of the virus are involved (Mansour, 2004). In conclusion, Uveitis has been one of the most common infections affecting the eye. It involves the inflammation of the middle layer of the eye known referred to as the Uvea. There are quite a number of predisposing factors to the ailment including exposure to toxins, infection, ankylosing spondylitis or rheumatoid arthritis. Research has shown that a cytokine called Tumor Necrosis Factor alpha (denoted as TNF-a) is one of the most crucial causes of Uveitis (Haraoui, 2005). High levels or excess production of these cytokines is known to induce the expression of adhesion molecules and chemokines, as well as other cytokines that are known to prolong inflammation.

In essence, researchers have been studying the use of TNF inhibitors as treatment for this ailment (Haraoui, 2005). These inhibitors include adalimumab, which studies have proved to be effective in treating the condition. Adalimumab tightly binds or adheres to the human TNF-a with a highly explicit affinity, thereby providing a block by interacting with the p75 and p55 cell-surface TNF receptors. In addition, adalimumab may, in the presence of a complement, lyse the surface TNF-expressing cells in vitro. An individual is usually required to take an injection of 40 mg per week, which may be increased depending on the prevailing circumstances (Mansour, 2007). It is worth noting that adalimumab comes with a number of side effects and even interacts with a number of medicines and vaccines. Some of the side effects include itching and pain, reduced capability of the immune system, reduced red cells and platelets in the blood, as well as hypersensitivity reactions. In some instances, an individual may undergo severe side effects such as cancer. This is especially in cases where he or she had rheumatoid arthritis, which is a one of the key risk factors for Uveitis (Mansour, 2007).

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