Comparison of treatment options of uveitis in juvenile idiopathic arthritis

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Comparison of Treatment Options of Uveitis in Juvenile Idiopathic Arthritis

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Abbreviations

ADA = Adalimumab

CARRA = Childhood Arthritis and Rheumatology Research Alliance

DMARD = Disease- modifying antirheumatic drug

ETN = Etanercept

FDA = Food and Drug Administration

IMT = immunomodulatory therapy

JIA = Juvenile idiopathic arthritis

MTX = Methotrexate

NSAIDs = Nonsteroidal anti-inflammatory drugs

TNF = Tumor necrosis factor

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1. Summary

Comparison of treatment options of uveitis in juvenile idiopathic arthritis

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Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in children and it affects approximately 1 in 1000 children worldwide. Children with JIA have an increased risk for uveitis and as many as 10-30% of children with JIA will develop uveitis. Severe or untreated uveitis can lead to long term complications and consequences, including cataracts, glaucoma and blindness; therefore treatment is of utmost importance. Topical corticosteroids and systemic immunosuppressants have been treatment of choice, however recently biologic agents have been used. An exploration of numerous clinical trials concerning the treatment of uveitis in JIA patients is necessary to conclude what the newest gold standard treatment should be. Specifically, a comparison of immunosuppressants alone versus a combination with biologic agents should be explored to deduce which is the most beneficial for treatment and if there is a difference in extent or type of side effects. Considering the high incidence level of this illness and the potential consequences if treatment is not provided, there is great importance in reviewing multiple clinical trials and concluding what the current treatment algorithm should be. This review aims to explore the current medical treatment of JIA –associated uveitis and the effectiveness and safety of the drugs involved.

Key words: Uveitis, JIA

2. Sažetak

Komparacija načina liječenja uveitisa u juvenilnom idiopatskom artritisu
Nataša Basrak

Juvenilni idiopatski artritis (JIA) najčešća je kronična reumatološka bolest kod djece i javlja se otprilike kod 1 od 1000 djece diljem svijeta. Djeca s JIA imaju povećani rizik za uveitis i čak 10-30% djece s JIA-om će razviti uveitis. Teški oblik uveitisa ili neliječeni uveitis može dovesti do dugoročnih komplikacija i posljedica, uključujući kataraktu, glaukom i sljepoću; Stoga je liječenje od najveće važnosti. Topički primjenjeni kortikosteroidi i sustavni imunosupresivi lijekovi su izbora, no u posljednje vrijeme koriste se biološki lijekovi. Analizom brojnih kliničkih ispitivanja vezanih uz liječenje uveitisa u pacijenata s JIA-om potrebno je zaključiti koji bi bio najnoviji standard u liječenju ove bolesti. Posebno, treba usporediti uporabu imunosupresiva samih u odnosu na kombinaciju s biološkim lijekovima kako bi se utvrdio koji je lijek najkorisniji za liječenje i utvrditi razliku u opsegu i vrsti nuspojava. S obzirom na visoku incidenciju ove bolesti i potencijalne posljedice neliječene bolesti, velika je važnost u analizi višestrukih kliničkih ispitivanja i zaključivanju što bi trebao biti trenutni algoritm liječenja. Cilj ovog preglednog rada je istražiti suvremeno liječenje JIA-udruženog uveitisa te učinkovitosti i sigurnost lijekova koji su uključeni u liječenje.

Ključne riječi: Uveitis, JIA

3. Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA), formerly juvenile rheumatoid arthritis (JRA) has several subtypes, in which there are varying numbers of joints involved, types of joints, systemic features, eye disease and association with human leukocyte antigens to name a few. The most common types are oligoarticular (<5 joints are involved) and polyarticular (≥5 joints are involved), which account in total about 90% of all patients with JIA (1).

The etiology is unknown and common characteristics of the illness include chronic synovitis, in which the synovium thickens and becomes hypervascularized and infiltrated with lymphocytes and inflammatory cytokines (1). There is also vascular endothelial hyperplasia and continuous erosion of articular cartilage and eventually, even the bony structures, due to the inflammation. Clinical features are often morning stiffness, fatigue, joint pain in later parts of the day, joint swelling, decreased motion, however no redness (1).

Regardless of the type of JIA, all the children are at risk for ocular issues, mainly chronic iridocyclitis or uveitis. There is an association between HLA-DR5, HLA-DR6, and HLA-DR8 and uveitis (1). Additionally, children with positive antinuclear antibody are at an even higher risk for chronic uveitis (1). A young female with oligoarticular JIA and positive antinuclear antibody has the highest risk of uveitis with an incidence of 80%.

Treatment of JIA focuses on decreasing inflammation and deformity, increasing mobility and preventing blindness. First choice is nonsteroidal anti-inflammatory drugs (NSAIDs). If treatment is not sufficient, second line medications such as hydroxychloroquine and sulfasalazine may be used. Biologic agents have also been used and include agents that inhibit TNF-alpha, including etanercept (ETN), infliximab and adalimumab (ADA). However, the side effects of these drugs are greater and include serious infection and possibly malignancy (1). Standard treatment of JIA consists of

NSAIDs, systemic glucocorticoids and/or disease- modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), however 30% fail to respond to treatment (2). Current US guidelines recommend “switching to biologic therapy in JIA patients with persistent moderate-to-severe disease activity, or drug intolerance, after four months of treatment with standard medical therapy” (3).

4. Uveitis

Uveitis is uveal inflammation that may involve one or all parts of the tract, including anterior uveitis (iritis), intermediate uveitis and posterior uveitis. JIA is primarily associated with anterior uveitis (4). The etiology is autoimmune with “predominant involvement of CD4+ T cells” (5). In oligoarticular JIA patients, chronic anterior uveitis has been particularly associated with HLA-DRB1*1104 and HLA-DPB1*0201 alleles (5). They are linked with a 7.7 times increased risk of chronic uveitis (5). While, HLA-DR1 has been proven to be protective (6).

Uveitis associated with JIA can be discovered at various points of the disease process. It can be asymptomatic until visual loss, thus regular ophthalmologic check-ups are necessary to allow prompt treatment. It is important to use a slit-lamp examination to look for anterior chamber inflammation. If diagnosed prior to visual loss, there are multiple clinical features. They can include photophobia, ocular pain, globe tenderness, brow ache, lacrimation, and/or ciliary flush (4). However, considering that the patients are juvenile, they may not report symptoms until vision loss is experienced.

Approximately 12-38% of JIA patients develop uveitis within seven years of disease onset, while 30-50% have structural complications present at diagnosis (7). Treatment should be aimed at decreasing “inflammatory activity, complications and risk factors for losing visual acuity” (8).

(A) Diagnosis of Uveitis

Children with JIA-associated chronic anterior uveitis are mostly asymptomatic thus routine ophthalmologic screening is prudent or else patients will present with serious complications. A predictor of visual outcome is the ocular condition during the first visit. Also, uveitis onset before or right after arthritis is a poor predictor of visual outcome.

Uveitis associated with JIA is usually bilateral, nongranulomatous and has a chronic relapsing course, but granulomatous disease does not exclude the diagnosis (9). “The most common complications include band keratopathy, cataract, posterior synechiae, glaucoma, maculopathy, hypotony and amblyopia” (9). Past cohort studies have found that rate of blindness can be as high as 30% but this can be reduced with regular screening and appropriate therapy (8).

5. Comparison of Treatment Options

(A) Introduction

Studies have found that JIA – associated therapy should be initiated when the AC cell grade is >0.5+ or when fibrin is found and “keratocytic precipitates with corneal edema and loss of visual acuity” (5, 8).

Current treatment frequently uses systemic immunosuppressive therapy and the commonest drug used is MTX. Oral corticosteroids can be used to gain rapid control of active uveitis(10). Corticosteroid use is not preferred long term due to risk of morbidity.

Recently, biological agents have been implemented as treatment and most common ones are tumor necrosis factor (TNF) -alpha inhibitors, but also drugs that target cytokine receptors, lymphocyte antigens, and lymphocyte co-stimulation signals. Multiple TNF- alpha inhibitors are available, including infliximab and ADA which are antibodies directed against the cytokine and ETN acts as a decoy receptor. Infliximab is a chimeric human-mouse monoclonal antibody against TNF- alpha and its administered intravenously (11). While, ADA is a fully human monoclonal antibody against TNF- alpha and is subcutaneously injected (11).

A wide range of treatment options are available since not all patients respond to the first line drug regimen (12). Recent advances to JIA – associated uveitis treatment include usage of biological drugs when patients are resistant to systemic immunosuppressive therapy or when conventional therapy cannot be used.

(B) Methotrexate

A retrospective cohort study concluded that use of immunosuppressive drugs controlled inflammation and thus there was a reduced risk of vision loss in patients with JIA- associated uveitis (13). However, the effectiveness of immunosuppressive drugs to change the course of the disease is still

questionable. A retrospective case series found that 82% of their patients had a significant decrease of uveitis after a minimal 3 month period of taking MTX (14). However, once MTX was discontinued due to inactive uveitis 69% relapsed after a mean time of 7.5 months and 46% relapsed within the first year of withdrawal (14). However, the relapse free time was much longer in patients who had been on MTX for more than 3 years, children who were 8 and older at withdrawal and those who had disease inactivity for longer than 2 years at withdrawal – all of which should be considered when deciding to take a patient off of MTX (14).

MTX use is not without risk. Sotoudehmanesh et al. found during a retrospective study that MTX hepatotoxicity is a common complication of long term use of MTX (15). The black box warnings for methotrexate include: hepatotoxicity, fibrosis, cirrhosis after prolonged use mainly, acute or chronic interstitial pneumonitis, nonproductive dry cough, diarrhea and ulcerative stomatitis, malignant lymphoma, tumor lysis syndrome, serious skin reactions and rashes and opportunistic infections (16, 17). Thus, it is important to prescribe MTX only when necessary and for as short a duration as possible.

(C) Current therapy algorithm

A 2011 study created a therapy algorithm for active uveitis. It is important to note that treatment of patients with anti-inflammatory therapy is not curative but solely symptomatic treatment to suppress inflammation (8). If the patient presents with poor prognostic factors, including glaucoma, cataract, then they should be started on topical corticosteroids and systemic corticosteroids (8). However, if there are no presenting symptoms then topical corticosteroids will suffice. This was referred to as step one. Step two begins after 12 weeks or earlier if required of “topical corticosteroids use 3 times daily or under systemic corticosteroid dosage of more than 0.15 mg/kg body weight” that does not provide relief or if new uveitis develops (8). This step includes addition of MTX or azathioprine to topical corticosteroids. Step 3 is initiated after 16 weeks or earlier if required and if there is still “inactivity or

reactivation or new inflammation –related complications" (8). This step indicates the addition of ADA or infliximab or cyclosporine. (8)

(D) Methotrexate + Biologics

In addition to the above therapy algorithm, Henderson et al. performed a cross-sectional cohort study to assess the current approach in treating JIA-caused uveitis and also idiopathic uveitis because there is no standardized approach (18). An analysis of patients with uveitis enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRAnet) registry was performed and focus was given to features, diseases complications and medications. This was necessary to perform seeing as there is a lack of current standardization due to only small, retrospective case series being available and not randomized, controlled trials (18).

Currently, oral and/or topical glucocorticoids, most commonly MTX, are the "first step in treatment of anterior, non-infectious uveitis in children" but long- term use should be avoided due to the side effects (18, 19). However, recently TNF inhibitors infliximab and ADA have been used as a treatment option of JIA – associated uveitis (20).

With this information regarding current practices, examination of the data from CARRAnet to assess actual treatment practices of JIA- associated uveitis was performed. CARRAnet is a registry of over 9000 children with rare pediatric rheumatologic conditions and contains clinical data, prior medication use and disease complications.

A total of 646 children with JIA uveitis were identified in the CARRA registry and the median age of disease onset was 2.8 years. 85% of patients received MTX (58% oral and 65% received subcutaneous); a total of 88% of JIA uveitis received a DMARD (18). At least one biologic agent was used in 56% of children and 55% of the time it was a TNF inhibitor (30% ADA, 25% ETN, 27% infliximab, 0.5% golimumab, 0.2% certolizumab) (18). However, the registry did not indicate if this treatment was specific for the arthritis or uveitis.

Current guidelines state that JIA- associated uveitis should be treated with systemic glucocorticoids only with “severe ocular inflammation, grades 3+ or 4+ or impending vision loss” but the registry does not indicate the level of ocular inflammation or level of vision loss (18, 21). Thus, it is not possible to conclude if the treatment guidelines are being followed or not (18). What can be concluded is that MTX is used in the treatment of JIA- associated uveitis and TNF inhibitors are the second most common (18).

Tappeiner et al. is a cohort study that used data from the National Pediatric Rheumatological Database in Germany to analyze the difference in treatment outcome of MTX alone, TNF inhibitors and a combination of the two in JIA- associated uveitis (22). 1801 patients were treated with MTX, 48 with TNF inhibitor monotherapy (38 with ETN, 5 with ADA and 5 with other), and 436 were treated with a combination of MTX and a TNF inhibitor (65 with ADA, 9 with infliximab and 362 with ETN) (22). Risk of uveitis was significantly decreased in all three treatment options compared to no DMARD treatment (22). Also, uveitis incidence was higher in patients treated with MTX and ETN (5.9%) compared to those treated with MTX and ADA (1.4%) (22). As well, patients that were treated within the first year of JIA diagnosis with MTX had a significantly lower risk of developing uveitis during the follow up period (22). The same was not found for patients that were treated early on with TNF inhibitors.

Current guidelines state starting MTX when NSAIDs and intraarticular corticosteroids are not sufficient and if response to MTX is insufficient or also in high-risk disease, addition of TNF inhibitors is recommended, particularly ADA due to the lower uveitis incidence compared to ETN (3, 22).

(E) Biologic Agents

The safety of biologics has been in question and multiple studies have examined the safety profile of various biologics. A source of concern while taking TNF- alpha inhibitors is the risk of tuberculosis reactivation. It is necessary to exclude existing infectious diseases and to make sure that

patients are up to date with immunizations prior to initiating TNF- alpha therapy (10).

In 2014, a case study was presented of a two year old with JIA – associated uveitis given ADA (23). She failed to respond to treatment with anti-inflammatories, low dose corticosteroids and MTX so she was placed on ADA, prednisone, and MTX and prednisone was tapered off after 1 month (23). She responded well to the new therapy with no side effects and displayed by good control of the disease, including resolved papilledema that had formed as a consequence of uveitis and was remission for 1 year (23). Another case involved a nine year old with an 8 year history of JIA and uveitis that had a relapse following two years of infliximab therapy (23). He was switched to ADA and MTX and he has remained in remission (23). The final case involved a five year old that had three flares of uveitis while on MTX alone (23). When ADA was added, two flares of uveitis responded well to local therapy but then was free of JIA and uveitis symptoms so both drugs were stopped and patient is in drug free remission (23). Thus supporting ADA therapy for uveitis in children.

A cross sectional retrospective analysis was performed in 2013, to assess ETN safety in Italian JIA patients (24). Patients given ETN after January 2000 were studied to assess the percentage still taking the drug versus those that were taken off and for what reasons. 1038 patients were analyzed in total, 40.7% were still taking ETN, 44.5% were discontinued and 14.8% were lost to follow-up (24). Median therapy duration was 2.5 years. Clinically significant side effects were reported in 27.8% and ETN was discontinued due to side effects in 9.5% (24). Side effects included new onset or recurrent uveitis (10.2%), infections (6.6%), injection site reactions (4.4%), neuropsychiatric (3.1%), gastrointestinal (2.4%), hematological disorders (2.1%), inflammatory bowel disease (10 patients developed), malignancy (2 patients developed) and one died of a fulminant streptococcal sepsis (24). However, on the other hand around half of the patients achieved complete disease remission under treatment with ETN (24). 41.8% to 48.6% of patients still taking ETN met formal criteria for inactive disease, 52.4% of patients that

discontinued ETN where in clinical remission and 55.8% of those lost to follow up where in clinical remission (24). Since ETN has a common appearance of new uveitis and relapse of uveitis it is not the most suitable biologic agent.

A prospective, comparative, multicenter cohort study found that ADA is more effective than infliximab at maintaining disease remission (11). 16 children were given ADA (12 of them had JIA) and 17 children were given infliximab (10 of them had JIA) (11). There was no difference between the groups regarding time to achieve remission and time to steroid discontinuation. 60% of children receiving ADA were in remission at the 40 month follow up, while 18.8% of children receiving infliximab were in remission at the same time (11). Also, a retrospective cohort study found that 11/18 patients relapsed when discontinuing infliximab treatment and those with JIA- associated uveitis relapsed at a median time of 76 days (25).

A 2013 study examined to see if there would be remission and safety differences when giving ADA as a first anti-TNF alpha choice to one group and giving it as a second anti-TNF alpha drug due to loss of efficacy of infliximab (26). It was concluded that there's better efficacy of ADA when it's the first anti-TNF alpha drug given (26). Group 1, which has 14 children (10 of whom have JIA), was given ADA as first anti-TNF alpha choice and they had a higher probability of steroid discontinuation within 12 months and they had higher disease remission than group 2 (26). Group 2, which has 12 children (7 of whom have JIA), was given ADA as a second anti- TNF alpha drug (26).

The U.S. Food and Drug Administration (FDA) has issued warnings concerning TNF alpha-blockers. FDA warns of an increased risk of infection of:tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, blastomycosis, pneumocystosis, hepatitis B, legionella, listeria and opportunistic infections (27). Suhler et al. performed a study of 23 patients being treated with infliximab for refractory uveitis (28). Some adverse events included pulmonary embolus, congestive heart failure, lupus like reaction in 2 and vitreous hemorrhage is 2 patients (28).

(F) Adulthood

All of the aforementioned studies have described treatment during childhood JIA- associated uveitis. However, once the children progress into adulthood, disease progression, uveitis presence and complications should be examined. Haasnoot et al. performed a retrospective chart review of patients with JIA –associated chronic anterior uveitis at their 18th, 22nd and 30th year of life (29). The study looks into 67 patients in total that were examined during periods between 1974 and 2015 (29). Treatment strategies changed around 1990 to 2000. Around 1990 MTX was initiated and in 2000 anti-TNF alpha agents were introduced, thus patients were split into two groups – one with onset of uveitis before 1990 and the other onset of uveitis after 1990 (29).

In regards to visual acuity, Haasnoot et al. concluded the amount of patients that were legally blind, had visual impairment or no visual impairment at 18, 22 and 30 years and then further divided them into those diagnosed before 1990 and those diagnosed after 1990 in both their best and worst eye (29). For ages 18 and 22, there was less legal blindness and visual impairment in those diagnosed after 1990 compared to those diagnosed before 1990 (29). No information was provided for those diagnosed after 1990 at the age of 30 thus no comparison can be drawn.

Regarding uveitis activity, 4% of patients at 18 years old were in remission for the whole year (29). 54% of patients had an episode of active uveitis at 18 years old, 73% were on systemic immunomodulatory therapy (IMT) and 81% were on topical steroids (29). The majority of patients diagnosed after 1990 were on systemic IMT whereas 17% of those diagnosed before 1990 were on systemic IMT at the age of 18 and a similar percentage at age of 22 (29). Since uveitis is present, it's complications also arise and thus a "relevant proportion of patients need cataract or glaucoma surgery during adulthood" (29).

Haasnoot et al. concluded that "introduction of MTX and anti-TNF alpha therapies have been important in the prevention of complications or even occurrence of uveitis in JIA- patients" (29). However, it is important to note the

effect on life that systemic IMT has. It results in more ophthalmologist visits and also a young woman wishing to become pregnant conflicts with its use (29).

6. Discontinuing Pharmacotherapy

Another topic of interest in JIA- associated uveitis is when therapy should be discontinued. As mentioned above, there are multiple side effects, some life threatening, for all of JIA- uveitis pharmacotherapy. General consensus amongst uveitis specialists is to attempt immunomodulatory therapy cessation after 12-24 months of disease remission (30).

Foell et al. performed a randomized clinical trial, in which patients were withdrawn from MTX at either 6 or 12 months of JIA remission (31). However, results did not provide clear evidence to discontinue pharmacotherapy at 6 or 12 months. At a 24-month follow up, 56.7% of patients, that had MTX withdrawn at 6 months, had relapsed, while 55.6% of patients, that had MTX withdrawn at 12 months, had relapsed (31). The median time to relapse for those at 6 months was 21.0 months and 23.0 months for those at 12 months (31). Thus, there is little difference between discontinuing MTX treatment at 6 months versus 12 months.

As detailed above, biologic agents also have serious and potentially fatal side effects thus they should also be discontinued when possible. Several studies above detail remission rates after discontinuation however there is not enough information regarding exactly when to discontinue other than uveitis specialists indicating that 12-24 months is best. Perhaps further scientific studies are necessary to explore this further.

7. Conclusion

It is of upmost importance to diagnose uveitis early so as to avoid any and all possible complications. Regular ophthalmologic examinations with slit lamp are imperative in all types of JIA, however especially the ones with a known higher incidence of uveitis. However, it is not uncommon for diagnosis to be overlooked due to lack of symptoms like redness, pain or light sensitivity because some children are not able to sufficiently communicate or due to chronic disease course (32).

Regarding safety, long term use of MTX is not advised due to its risk of morbidity and suppression of immune function. However, it is excellent regarding disease control. In regards to biologic agents, as mentioned it is imperative to exclude existing infectious diseases and to make sure that patients are up to date with immunizations prior to starting TNF alpha inhibitors.

Evidence shows that early use of systemic immunosuppressants is key to decrease intraocular inflammation. Biologic agents have been proven to be beneficial as additional treatment if immunosuppressants do not provide relief. There is a lack of evidence to support the sole use of biologic agents. Based on all of the aforementioned studies, MTX should be started upon JIA diagnosis. Treatment with MTX is not a means of curing the disease, but rather it is symptomatic treatment. If disease activity is severe or treatment is insufficient, biologic agents, preferably ADA, should be added.

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10. Biography

Nataša Basrak was born in Bosnia and Herzegovina and moved to Canada at a young age. Upon graduating from high school, she went to Queen's University and graduated with a Bachelor of Science with Honors: Life Science major and World Language Studies minor. Afterwards, she came to the University of Zagreb: Medical Studies in English. Nataša has had an active role in student life, including being class representative on the university's student council and being a demonstrator for her younger colleagues in the course History Taking and Physical Examination for multiple years. She is particularly interested in Ophthalmology and Cardiology and hopes to continue pursuing these passions in her future medical career.