• Meta-Analysis •

Effects of anti-TNF biologic drugs on uveitis severity in Behçet patients: systematic review and Meta-analysis

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Received: 2021-05-28 Accepted: 2021-09-15

Abstract

● **AIM:** To investigate effects of anti-TNF biologic drugs on uveitis severity (comparing visual acuity logMAR levels) in Behçet patients.

● **METHODS:** Three databases PubMed, Scopus, and the Web of Science were searched for qualified papers focusing on the anti-TNF-α factors treatment in Behçet's disease (BD)-associated uveitis. Studies that were designed pre and post anti-TNF drug treatment, were selected. After determining the search strategy for this study, the relevant data were extracted.

● **RESULTS:** The initial search was performed in the target databases and a total of about 1458 articles were found. Fifteen articles were selected for systematic review and only 12 of them had inclusion criteria for Meta-analysis (with visual acuity data). The mean dose of prednisolone before and after biological treatments was reported in 5 studies (28.56 and 7.56 mg/kg, respectively). Also, the preliminary results indicate a significant reduction in visual acuity logMAR levels (MD=-1.5 IU/L, 95%CI: -2.1, -0.01).

● **CONCLUSION:** Biological drugs significantly reduce the dose of prednisolone and affect visual acuity values.

● **KEYWORDS:** anti-TNF drugs; Behçet's disease; infliximab; uveitis; visual acuity

DOI:10.18240/ijo.2022.05.19

Citation: Abolhasani S, Khabbazi A, Hosseini F, Gholizadeh-Ghaleh Aziz Sh, Alipour Sh. Effects of anti-TNF biologic drugs on uveitis severity in Behçet patients: systematic review and Meta-analysis. *Int J Ophthalmol* 2022;15(5):813-819

INTRODUCTION

Behçet's disease (BD) was first discovered by Hulusi Behçet[1]. The geographical distribution of BD is related to the Silk Road rout. The disease is widespread in Middle Eastern, Far Eastern and Mediterranean countries such as Iran, Turkey, Tunisia, China, and Japan[2]. The highest incidence of BD is in Turkey (80 to 370 patients per 100 000 population). The prevalence of the disease in Japan is about 13.5 per 100 000 and in Iran 80 per 100 000[2]. It is a vasculitis associated with oral and genital ulcers, skin lesions and ocular involvement[3]. Ocular involvement is in the form of recurrent non-granulomatous uveitis that can affect the anterior and posterior chambers of the eye. Uveitis is usually bilateral[3]. However, the intestine and the central nervous system can also be affected[4].

Management and treatment of BD is a serious challenge due to different clinical aspects. Therefore, treatment should be proportional to the patient's condition and severity of clinical symptoms[5]. Colchicine and non-steroidal anti-inflammatory drugs are often used to treat joint and mucosal involvement. However, more aggressive methods and immune suppressive agents are needed to treat severe symptoms such as uveitis, retinal vasculitis, neurological and gastrointestinal involvement[6]. Current treatment focuses on reducing inflammation and controlling the immune system. For severe manifestation of the disease, high dose corticosteroids are used[7].

BD patients have high levels of proinflammatory cytokines such as IL-1, IL-2, IL-6, tumor necrosis factor (TNF-α), IL-12, IL-17, IL-18, and IL-23R[8-13]. TNF-α is an inflammatory cytokine that plays a role in homeostasis and immune response and in fact, it plays a major role in autoimmune diseases pathogenesis[14-15]. This cytokine is encoded in the class 3 region of the HLA complex adjacent to HLA-B[16]. TNF-α is secreted by many types of cells such as macrophages, monocytes and lymphocytes[14]. Anti-TNF drugs are a group of medications that suppresses the physiologic response to

TNF-α. The medications in this class include infliximab, etanercept, adalimumab, certolizumab pegol and golimumab. Infliximab, adalimumab, and golimumab are monoclonal antibodies against TNF-α. Etanercept is a soluble, divalent TNF-α receptor that binds to TNF-α to prevent it from binding to its receptor on the cell. Certolizumab pegol is the antigen-binding fragment (Fab') of a humanized monoclonal antibody that has been conjugated to polyethylene glycol. Induction of antibodies against TNF is largely dependent on its structure, chimeric drugs have a higher capacity to stimulate the immune system than human drugs[17].

The essential purposes in the management of patients with Behçet's uveitis are fast elimination of visual inflammation, avoidance of recurrent attacks, getting of whole remission, and maintenance of vision. Corticosteroids are generally used for the treatment of episodes of inflammation; however, their long-term use is associated with unacceptable side effects. Relapses are normal in the setting of steroid mono-therapy, and conventional immunosuppressive drugs have usually been used for long-term treatment[18].

The combination of azathioprine and cyclosporine is more impressive than is immunotherapy with either factor, or combination therapy is used as a severe immunosuppressive regimen for the treatment of patients with severe Behçet's uveitis[19]. In addition, we did not find any studies comparing infliximab with steroids. However, in some studies, infliximab was compared with cyclosporine, and the results showed that following the use of infliximab, the conditions of ocular inflammation were greatly reduced[20].

Anti-TNF drugs that has been approved for treatment of rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis and has been used for the treatment of uveitis in BD with promising results[21-22]. In general, anti-TNFs such as infliximab have been used to treatment uveitis, and anti-TNFs such as etanercept have been used to treat skin lesions[23]. Some studies have suggested that long-term use of biologic drugs can lead to infection in some patients. However, some other studies have shown that no side effects lead to infection of the skin, soft tissues and joints[24]. In some other studies, it has been reported to cause cancer in people who have taken these drugs for a long time. But in general, none has been proven[25]. However, due to inconsistent results of the present studies and the lack of systematic study, this study is intended to evaluate the therapeutic effects of anti-TNF agents in BD patients with ocular involvement.

MATERIALS AND METHODS

Search Strategy After determining the search keywords, including Behçet's disease, Behçet's syndrome, adamantiades-Behçet's disease, anti-TNF agents and uveitis, they were searched both using MeSH keywords and freely in the databases of MEDLINE, Scopus, CINHAL, Psycoinfo, Cochrane Library, Proquest. Iranmedex, SID, IranDoc, Magiran databases were also searched for information in Persian. In addition to the above databases, the list of selected study resources as well as related conferences was searched manually.

The articles and documents obtained from the search were screened in several stages in terms of title, abstract and full text, and the final studies with inclusion criteria were selected. The studies were evaluated by 2 experts and using a checklist (PRISMA) in terms of the types of bias risks (selection, performance, report, attrition, *etc*.) as well as content, critique and low-quality studies were discarded. Also, in case of disagreement between the experts, the third person was used and a group discussion was held. Relevant data were then extracted from the studies using a designed table.

Inclusion and Exclusion Criteria All articles were searched until May 2020 and studies were included in our research that met the inclusion criteria and included: 1) were published by May 2020; 2) studies were designed pre and post anti-TNF drug treatment; 3) were consistent in terms of keywords (in the field of BD, anti-TNF drugs, visual acuity, conflict and ocular attack); 4) contained information of the original article type; 5) had sufficient information such as best-corrected visual acuity (BCVA) or decimal or visual acuity logMAR score.

Exclusion criteria also included: 1) in terms of keywords in the title and abstract screening stage did not match; 2) review and duplicate studies were excluded; 3) studies unrelated to Behçet and eye involvement and lacked visual acuity score; 4) non-human studies (for example in the mouse).

According to the contents mentioned in this section, in the first stage after the initial search, the number of articles included in the study was 1504, of which 523 were duplicate articles (981 articles remaining). Finally, according to the mentioned criteria, only 15 articles were found to be completely relevant, of which 12 articles were included in the analysis related to the visual acuity criterion (Figure 1).

Extract Data After identifying the final articles, the articles were sorted by publication date. Before extracting the data, the tables required for this study were designed based on the required criteria in the extraction table in excel software environment. Then, two authors separately and independently extracted the required data from the final selected articles based on pre-prepared tables.

These data include general data of articles (name of the first authors of the articles, name of the country of study, year of study, sample size, age of individuals, length of treatment, and length of follow-up), data related to interventions (type of drug used, drug dose, names of other drugs (steroid and non-steroidal drugs), response data (BCVA score, ocular attacks, prednisolone dose pre and post anti-TNF drug used).

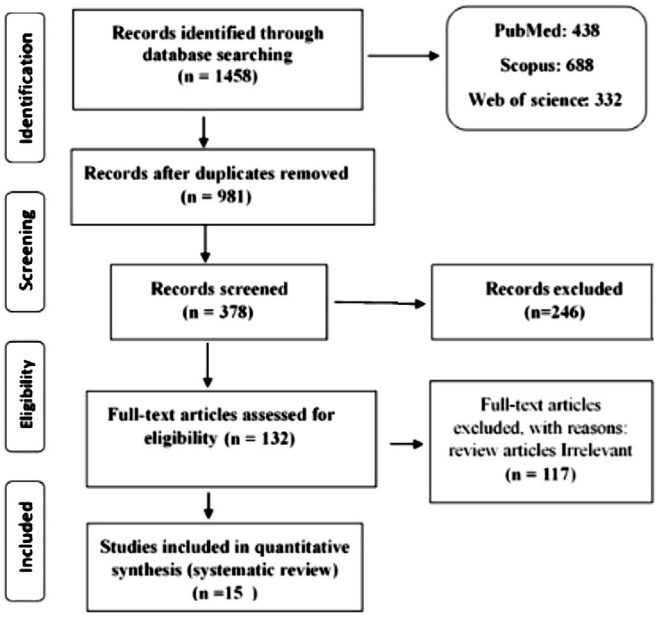

Figure 1 Search strategy The initial search results showed more than 1458 articles, but in the end 15 articles were selected for systematic review and 12 articles for Meta-analysis.

After fully extracting the data related to our articles, it was found that only the visual acuity index has been reported in most articles and is common to them and we lastly selected this index for the Meta-analysis. Finally, in case of discrepancies between the data, it was discussed until the same result was reached.

Quality Evaluation We assessed the quality of the involved studies using the Cochrane Collaboration's tool for assessing the risk of bias[26]. In this reading, selected studies were judged based on the following criteria: bias related to patient selection ("selection bias") which is determined based on the complete description of patient selection and their inclusion and exclusion criteria. If patients are carefully selected, they will be considered low risk in terms of bias risk. Measurement bias, which in this study is related to methods of measuring ocular involvement and ocular inflammation and score related to visual acuity. If precise methods are used, the risk is considered low. Follow-up bias, which refers to the length of the follow-up period. If it is mentioned in full detail, the risk is low in terms of bias. Exposure bias was considered as changes in ocular inflammation in patients. If the values related to visual acuity, eye inflammation and eye attacks are reported with great accuracy, it is reported as low risk. Finally, confounding bias is related to the data analysis and results. If the confounding factors such as gender, age, and drug use are carefully observed during the analysis of visual acuity and other factors related to eye inflammation, that study is considered low risk in confounding bias.

Statistical Analysis Data for this study were extracted using a pre-designed table. Then, using comprehensive Meta-analyzed CMA.2 software, the data were analyzed by random effect method and the heterogeneity of the studies and their distribution was evaluated and Forrest plot and Funnel plot diagrams were presented.

RESULTS

Findings from Systematic Review

Included studies After systematic review of articles, according to inclusion and exclusion criteria, finally 15 related articles were found, of which 12 articles were included in the Meta-analysis. One study was conducted in the Africa, six studies in European countries, and eight study in Asia. Of the 15 articles found, 9 articles examined the effect of infliximab and 4 articles about adalimumab and two others as a combination of two drugs. In these studies, the dose of infliximab was 5 mg/kg and adalimumab was 40 mg/subcutaneous/2wk. The mean age of the samples was 31.0y and the mean duration of illness and follow-up were 7.88y and 16.72wk, respectively. In these studies, the average duration of use of biological drugs was 18.21mo. The mean dose of prednisolone before and after biological treatments was reported in 5 studies and was 28.56 and 7.56 mg/kg, respectively.

Description of studies The electronic search, conducted until May 2020, resulted in 1458 abstracts, of which 378 abstracts were reviewed. Of those, 118 full texts were read and 15 found to be eligible (of these, 15 articles were selected for systematic review and among them 12 articles had the necessary properties for Meta-analysis). The reference lists of all 12 case-control were searched for relevant articles. Full texts of the major reviews found were read and their reference lists searched. The study characteristics of the patients enrolled in these studies are summarized in Table 1[3,27-40].

We measured risk of bias using the Cochrane Collaboration's tool for measuring the risk of bias in randomized trials. We classified bias according to five domains: sample selection bias, measurement bias, follow-up bias, exposure (ocular response) bias, and confounding (correlation) bias. We defined risk of bias as low, high, unclear risk. In most of the studies we reviewed, the inclusion and exclusion criteria were clearly mentioned, and most of them were in the low group. Most studies on the method section and method of assessment the severity of ocular inflammation and visual acuity score were fully explained. Therefore, these options were placed in the low-risk bias group.

The studies also showed that the follow-up range and length of patients is either fully explained or incomplete. Because of this, they were either low or high risk in terms of follow-up bias. The bias of ocular response (exposure bias) was fully focused in most studies. Therefore, the bias of this option was considered low risk. Finally, in most studies, confounding factors such as gender, age, and medication use were carefully

Table 1 A summary of included study characteristics for trial quality-assessment score

ID	First author (y)	Ref.	Country	Sample size	Type of drug used	Mean age (y)	Follow up (mo)	Disease duration (y)	Duration of drug use with anti-TNF (mo)	No. of ocular attacks (flare/patient/y)		Visual acuity (logMAR)		Dose of prednisolone (mg/d)	
										Before	After	Before	After	Before	After
1	L. Niccoli (2007)	27	Italy	12	Infliximab	33±12.8	12	11±14.5	12	40	5	0.7±0.1	0.32± 0.4		
2	Annarita Giardina (2011)	28	Italy	21	Infliximab	36±2.5	12		12			0.4±0.2	0.1±0.08		
3	Atsushi Yoshida (2012)	29	Japan	29	Infliximab	31±8.4	12		6	8.2±6.3	1.6±3.1	0.57±0.59	0.48±0.56		
4	Ilknur Tugal-Tutkun (2005)	3	Turkey	13	Infliximab	28.2±6.8	12	6.3±3.6	12	2.4±0.7	1.0±0.8	0.35±0.3	0.23±0.16	27.6±17.1	14.1±7.7
5	Sultan Al Rashidi (2013)	31	Saudi Arabia	19	Infliximab	25.6±7.8	44.1±36.5		55.7±22.8			0.84±0.8	0.3±0.4		
6	Mary Ho (2019)	32	China	5	Adalimumab	14±4	24-53	7±5.0	12			071±0.63	0.17±1.05	40	7.5
7	Iris Deitch (2018)	33	Israel	24	Infliximab & adalimumab	9.3±4.0	12		30.88±18.2			0.45	0.25		
8	Ayman K. El Garf (2017)	34	Egypt	20	Infliximab	31.8±9.1	12	8±6				1±0.09	0.1±0.2	20-40	
9	Emanuela Interlandi (2014)	35	Italy	12	Adalimumab	24.3±8.6	21±9.63	9±5.86		2	0.42	0.45	0.22	26.9	3.3
10	Claudia Fabiani (2017)	30	Italy	40	Adalimumab	41.9±11.9	12	9.92±7.80	12	2	0.09	0.14	0.09		
11	Tsutomu Sakai (2013)	36	Japan	20	Infliximab	45±14	12			3.7±2.2	0.3±0.9				
12	Sho Ueda (2018)	37	Japan	44	Infliximab	39.1	24	4	12-24	3.28±0.32	0.45±0.18				
13	Ahmed Bawazeer (2010)	38	Saudi Arabia	11	Adalimumab	28	10.8		24					18.3	7.9
14	Hiroshi Keino (2011)	39	Japan	14	Infliximab	38	19		12	4	1.2				
15	Belén Atienz-Mateo (2019)	40	Spain	Infliximab 103 adalimumab 74	Infliximab & adalimumab	Infliximab 40.4±10.1 adalimumab 38.7±1.3	12		12		1.1 in infliximab 1.6 in adalimumab	Infliximab 0.5 adalimumab 0.4	0.4 2.6	30	5

Figure 2 The risk of bias assessment of the included studies Most of the studies in terms of bias are low risk.

considered during the analysis of visual acuity and other factors associated with ocular inflammation. For this reason, in most of them, low-risk bias was considered. The risk of bias in each included study is summarized in Table 2 and Figure 2.

Findings from Meta-Analysis Data was entered in Comprehensive Meta-Analysis (CMA) 2.2 (BioStat Inc., US) and random-effect models were used. Assessment of risk of bias in included studies has been considered. The visual acuity logMAR score as the primary outcome variable was expressed as continuous variables. Standard deviation was calculated using actual *P*-values obtained from *t*-tests quoted by Cochrane. For every study, we calculated the mean difference (MD) for the primary outcome visual acuity logMAR score using 95% confidence interval (95%CI). The outcome measures were pooled by use of the random-effect model. Heterogeneity was calculated using Cochrane's *Q* statistic and quantified using the I^2 statistic. These indicated the proportion of variability across studies due to heterogeneity, rather than sample error. In the case of missing data, efforts to contact authors were made.

The preliminary results indicate a nonsignificant reduction in visual acuity logMAR score (MD=-1.5 IU/L, 95%CI: -2.1, -0.01). However, significant heterogeneity was revealed among studies (Q=154.97, I^2=92.9%, P<0.001). Despite a high I^2, results were pooled, as examination of these studies on a Forest plot indicated that the individual trial results were consistent in the direction of the effect (*i.e.*, MD and confidence intervals largely fell on one side of the null line; Figure 3). Characteristics of age, sex ratios, and baseline visual acuity were similar across all trials. Table 1 highlights the characteristics of the included studies.

Asymmetry assessment of the funnel plot was conducted for publication bias only to showcase the sample interventions. There was a slight asymmetry in Begg's funnel plot, we did not find any evidence of publication bias for visual acuity logMAR (Egger's test t=2.54, P=0.05, Begg's test Z=0.6, P=0.54; Figure 4).

Table 2 The risk of bias assessment of the included studies

Author (y)	Sample selection bias (inclusion and exclusion)	Measurement bias (methods)	Follow-up bias	Exposure bias (ocular response)	Confounding bias (correlation)
L. Niccoli (2007)	Low	High	Low	Low	Unclear
Annarita Giardina (2011)	Low	Low	High	Low	Low
Atsushi Yoshida (2012)	Low	Low	Low	Low	High
Ilknur Tugal-Tutkun (2005)	Low	Low	Low	Low	Low
Sultan Al Rashidi (2013)	High	High	Low	Low	High
Mary Ho (2019)	High	Unclear	Low	High	High
Iris Deitch (2018)	Unclear	Low	High	Low	High
Ayman K. El Garf (2017)	Low	Low	High	Low	Low
Emanuela Interlandi (2014)	High	Low	Low	Low	Low
Claudia Fabiani (2017)	Unclear	Low	Low	Low	Low
Tsutomu Sakai (2013)	High	High	High	High	Unclear
Sho Ueda (2018)	Low	Unclear	Low	Low	Low
Ahmed Bawazeer (2010)	Unclear	Unclear	High	Low	Low
Hiroshi Keino (2016)	Unclear	Low	Low	Low	Low
Belén Atienza-Mateo (2019)	Unclear	Low	High	Low	Low

The studies were reviewed for publication bias in 5 steps and categorized as high, low, and unclear in terms of risk.

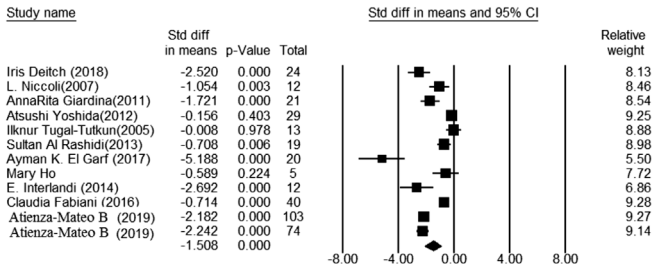

Figure 3 Characteristics of studies included in the Meta-analysis Forest plot of the effect of anti-TNF biologic drugs on uveitis severity in BD. A random-effects model for the OR with 95%CI was used to detect an effect of anti-TNF biologic drugs on uveitis severity in BD. BD: Behçet's disease; OR: Odds ratio; 95%CI: 95% confidence interval.

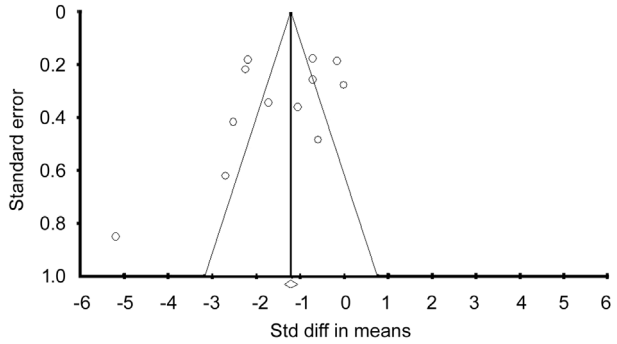

Figure 4 Begg's funnel plot for publication bias analysis of the effect of anti-TNF biologic drugs on uveitis severity in BD Symmetry in Begg's funnel plots demonstrates the absence of publication bias in the studies investigating the the effect of anti-TNF biologic drugs on uveitis severity in BD. BD: Behçet's disease.

DISCUSSION

The visual prognosis in BD is affected by severe recurrence of uveitis. Recurrent attacks of ocular inflammation lead to structural changes that may lead to visual impairment and even blindness in patients if not treated promptly and appropriately. The main goal of Behçet's uveitis management is to quickly eliminate inflammation inside the eye, prevent recurrent attacks and maintain vision in these patients. TNF-α is a factor that plays a pivotal role in the development and maintenance of the inflammatory response, even though the specific etiopathogenesis of BD has not yet been elucidated but many experimental studies have shown that TNF-α plays an important role in the progression and persistence of ocular inflammation in BD[41-42]. Therefore, in order to better understand which anti-TNF drugs have an effective therapeutic role in BD, we conducted this systematic review and Meta-analysis of data and pooled results.

The TNF-α is a pro-inflammatory cytokine which can adjust immune cells' activity in autoimmune diseases. Since BD is a kind of autoimmune disease, therefore, TNF-α plays a significant role in causing inflammation in BD[30]. Research shows that high levels of TNF-α and its receptors are present in the serum or plasma of BD patients along with other proinflammatory cytokines[31]. Accordingly, blocking the TNF-α pathway can be considered as the first or second-line valid treatment in BD patients with ocular symptoms and uveitis. Anti-TNF drugs as a new therapeutic approach are the strategic alternative to traditional safety immunosuppressant[43-44] while the results of infliximab have been very encouraging for the treatment of severe uveitis in BD[45-46].

The researchers showed that anti-TNF-α regulates peripheral blood CD4+ T cells in patients with posterior intraocular inflammation, which is associated with improved visual function. In one study, researchers have been found that infliximab injections in patients with BD reduced the number

of TNF-secreting peripheral blood mononuclear cells[47], which in turn reduced eye attacks and improved vision in patients[37]. This study confirmed the efficacy of anti-TNF therapy (infliximab or adalimumab) for treating refractory uveitis associated with BD. Also, the results related to the number of ocular inflammatory attacks in these patients have been shown that the number of attacks after the addition of biological anti-TNF therapies has decreased significantly as shown in earlier studies. Since the use of some drugs can interfere with the results of the study, so these studies were not included in the results and were excluded from our study. However, in most studies, patients have used the same drugs to treat the disease, and in the end, only the results of prednisolone, which had a decreasing trend, have been reported in some studies[30,32]. The results of some previous studies on the effects of these drugs may seem contradictory. One of the main reasons for the contrary results of the studies may be due to the fact that the patients studied in this research used different immunosuppressive drugs, some patients have used corticosteroids, and others have used drugs such as colchicine, azathioprine, and cyclosporine. Also, the dose and duration of drugs use have varied in different people, and all of these can affect the final results of these studies. In general, most treatments are used to reduce the dose of steroid drugs, which these drugs (anti-TNF) have also been associated with a significant reduction in the use of steroid drugs.

One of the main limitations of this study may be the relatively low sample size in the studies. Other limiting factors include confounding factors such as patients' age, medications used, type of medication, and dose of medication before biological drugs are added. However, in some studies, these factors were considered as confounders and the final results were reported.

In conclusion, however, the overall results of this study show that the use of biologic drugs (anti-TNF drugs) along with other therapeutic drugs, has been effective on patients' visual acuity and has led to a significant improvement in them. Also, the amount of eye attacks in them has been significantly reduced. In addition, since the long-term use of corticosteroid drugs can be harmful, simultaneous use of biological drugs can reduce the dose of prednisolone.

ACKNOWLEDGEMENTS

Conflicts of Interest: Abolhasani S, None; **Khabbazi A,** None; **Hosseini F,** None; **Gholizadeh-Ghaleh Aziz Sh,** None; **Alipour Sh,** None.

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