Systematic Review and Meta-Analysis

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Efficacy and safety of immunomodulatory drugs in patients with anterior uveitis

A systematic literature review

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Abstract

Background: To assess the efficacy and safety of immunomodulatory drugs in patients with noninfectious anterior uveitis (AU).

Methods: Systematic review of studies were retrieved from Medline (1961 to March 2016), Embase (1961 to March 2016), and Cochrane Library (up to March 2016), and a complementary hand search was also performed. The selection criteria were as follows: (population) noninfectious AU patients, adults; (intervention) immunomodulatory drugs (any dose, regimen, route of administration, duration of treatment); (outcome) control of inflammation, steroid-sparing effect, AU flares, adverse events, and so on; (study design) systematic literature reviews, randomized controlled trials, and observational studies. The study quality was assessed using the Jadad scale and according to The Oxford Centre for Evidence-based Medicine (update 2009).

Results: We included 13 studies of moderate-poor quality, with a mean duration from 5 months to 20 years, and number of AU patients ranging from 9 to 274. Patient's demographic and clinical characteristics were very heterogeneous. In most cases, uveitis anatomic classification criteria and outcomes definitions were unclear. Some of the studies only included AU patients with a systemic disease associated, mostly spondyloarthritis, others, mixed populations (idiopathic and systemic disease associated patients), and in some articles this data is not described. We found that methotrexate, cyclosporine A, azathioprine, adalimumab, and golimumab might prevent AU flares, improve ocular inflammation and visual acuity, and decrease systemic steroids doses.

Conclusions: Although there is a lack of robust evidence, methotrexate, cyclosporine A, azathioprine, adalimumab, and golimumab might be effective in AU patients.

Abbreviations: ADA = adalimumab, AE = adverse events, AS = ankylosing spondylitis, AU = anterior uveitis, AZA = azathioprine, CsA = cyclosporine A, GLM = golimumab, g = gram, mg = milligram, MTX = methotrexate, RCT = randomized controlled trials, SLR = systematic literature review, SpA = spondyloarthritis, SSZ = salazopyrin, TNF-α = tumor necrosis factor-alpha.

Keywords: anterior uveitis, immunomodulatory drugs, systematic review

1. Introduction

Anterior uveitis (AU) is the most common pattern of uveitis, accounting for 50% to 92% of uveitis cases in western countries.[1–3] A significant proportion of patients have no evidence of an underlying disorder and are labeled as idiopathic, but there is also an important percentage of patients with an associated systemic disorder such as spondyloarthritis (SpA).[4]

AU usually responds well to topical corticosteroids.[5] However, there are cases, especially those associated with systemic disorders that may require additional drugs. For example, HLA-B27 AU, is typically more severe, recurrent, and associated with a higher incidence of ocular complications,[6] including wide anterior and posterior synechiae, secondary glaucoma, and cystoid macular edema.[7,8] For these patients, periocular corticosteroid injection is an option as well as systemic corticosteroid therapy.[9] Corticosteroids alone might help decrease ocular inflammation during exacerbations. However, they are not sufficient for many cases of chronic uveitis and do not prevent further relapses. Besides, long-term corticosteroid therapy also incurs significant risk of unacceptable adverse events (AE) like cushingoid changes, iatrogenic diabetes, osteoporosis, and hypercholesterolemia.[10]

On the other hand, immunomodulatory drugs have been widely used in patients with uveitis for decades. Classical immunomodulators such as salazopyrin (SSZ) or methotrexate (MTX) have been shown effective in controlling ocular

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inflammation, preventing AU flares and potential visual loss, and in decreasing the corticosteroids need.[11,12] Nevertheless, patients could be refractory or intolerant to these classical drugs. In recent years, the use of off-label biologic agents, particularly tumor necrosis factor-alpha (TNF-α) inhibitors, has spread worldwide for treatment of patients with noninfectious uveitis resistant to traditional immunosuppressors showing encouraging results.[13] This provides new options for the treatment of AU, which, in turn, calls for the need of updating the evidence in order to establish a framework for supporting treatment recommendations.

Finally, taking also into account that therapeutic decision-making in infectious and malignant AU is much less controversial, the aim of this paper was to perform a systematic and critical review of the literature on the use of immunomodulatory drugs in adult patients with noninfectious and nonmalignant AU.

2. Methods

In context of a clinical practice guideline for the management of uveitis, a systematic literature review (SLR) was performed to address the experts' question on the efficacy and safety of current available immunomodulatory drugs in patients with noninfectious nonmalignant AU. In accordance with the experts, a review protocol was established for this purpose and we followed the indications of the PRISMA statement. As this is an SLR, not an interventional study, an ethical approval was not necessary. The same way patients were not included and therefore informed consent was not given.

2.1. Search strategy

The studies were identified by sensitive search strategies in the main medical databases. We have listed the search strategies in the supplementary data. For this purpose, an expert librarian collaborated and checked the search strategies. The following bibliographic databases were screened: Medline (PubMed) and Embase (Embase.com) from 1961 to March 2016, and The Cochrane Library (including Cochrane Central Register of Controlled Trials, i.e., CENTRAL and the Database of Reviews of Effectiveness, i.e., DARE) up to March 2016. We used specific MeSH headings and additional keywords to identify studies on AU and different types of immunomodulatory drugs. The strategy combines disease and treatment terms as listed previously and a controlled vocabulary for describing any of them. All the retrieved references were managed in Endnote X5 (Thomson Reuters).

Finally, a hand search was completed by reviewing the references of the included studies, and all the publications or other information provided by the experts related to SLR were also examined.

2.2. Selection criteria

The studies retrieved by the search strategies were included if they met the following pre-established criteria: Patients had to be diagnosed with active noninfectious nonmalignant AU, 18 years or older, taking an immunomodulatory drug, including SSZ, MTX, cyclosporine A (CsA), azathioprine (AZA), leflunomide, chlorambucil, cyclophosphamide, mycophenolate, and tacrolimus, or biologic therapies (anti-TNFα drugs and others). There was no restriction regarding the type of drug, dose, route of administration, concomitant use of other drugs, or treatment duration. Different outcomes were considered such as control of inflammation, steroid-sparing effect, visual acuity, reduction of the number of uveitis flares, or AE. Only SLR, randomized controlled trials (RCT), or observational studies (study sample size ≥10 patients) were included as well as studies in English, French, or Spanish language. Studies analyzing patients with uveitis from different or various anatomic sites other than anterior segment were excluded unless they performed sub-analysis with those with AU.

2.3. Screening of studies, data collection, and data analysis

Screening of studies, data collection, and analysis was performed by 2 reviewers (AG and EL). First, both reviewers screened the titles and abstracts of the retrieved articles for selection criteria independently. This process was done in 20 minutes sessions. If, while doing this, the reviewers found any discrepancy between them, then, a consensus was reached by asking a third reviewer (LC). The same process was afterward undertaken. The articles from the previous selection process were read in detail, and at the end of this phase a list of included studies was established.

The collection of data from the included studies was carried out by two reviewers independently for every article. As in previous processes, in case of discrepancies, a consensus was reached by looking at the original article or by asking the third reviewer (LC). Articles that did not fulfil all the inclusion criteria or that had insufficient data were excluded.

To grade the quality and risk of bias, we used the Jadad score[14] for RCT and a modification of The Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2011 update,[15] in which articles are classified as follows: systematic reviews of RCT with homogeneity; individual RCT with narrow confidence intervals; trials in which all patients get harm or none does; systematic reviews of cohort studies with homogeneity; individual cohort study, or low quality RCTs; "Outcomes" Research and Ecological studies; systematic reviews of case-control studies with homogeneity; individual case-control study; case-series and poor quality cohort and case-control studies; and expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles."

Evidence tables were produced. Descriptive analyses were performed. To describe the included article samples, we used the distribution of frequencies, the mean and standard deviation, or the median and interquartile range, depending on the distribution. Comparisons were performed using the Student *t* test or the chi-square test. Meta-analysis was only planned in case enough homogeneity was present among the included studies.

3. Results

The search strategies retrieved 2166 references (Fig. 1), of which 425 were duplicates. After the selection by title and abstract, 98 references were selected for review in detail. After this process, 85 were excluded mainly due to lack of data regarding AU patients or to the absence of a clear anatomic classification of the uveitis (Table 1).[12,13,16–98] As a result, 13 articles (Tables 2 and 3) were finally included.[11,99–110] The articles found in the hand search were also excluded.

The quality of the included articles was in general poor or moderate. We found 2 RCTs,[11,105] the rest were observational studies. Their mean study duration varied from 5 months[108] to 20 years,[102] and the number of AU patients from 9[12] to 274,[108] in whom clinical characteristics were also very

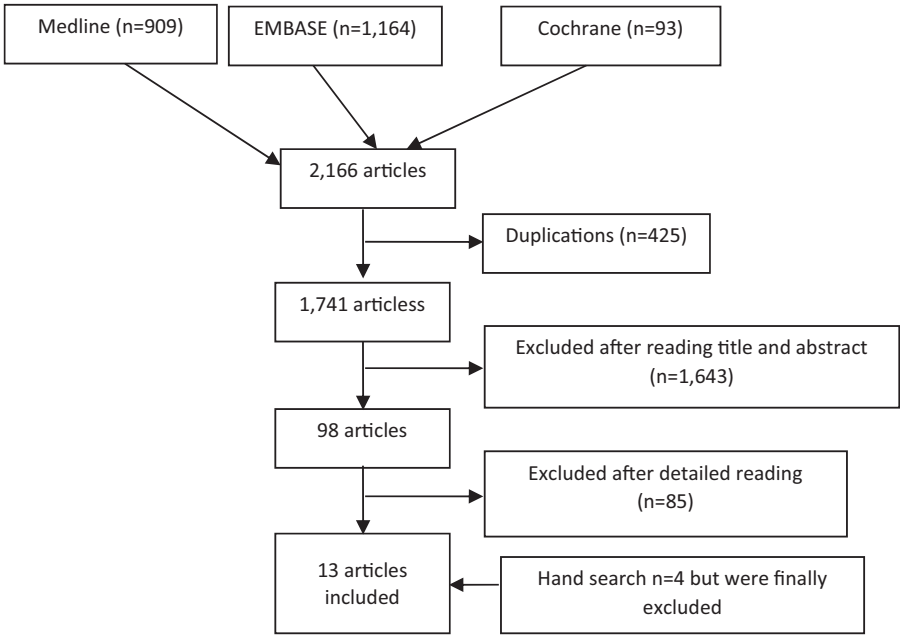

Figure 1. Studies flow chart.

heterogeneous (see Table 1). In most cases, criteria to define the anatomic classification of uveitis and efficacy definitions were not clear. Besides, some of the studies only included AU patients with a systemic disease associated, basically SpA,[11,100,102,108,110] others mixed populations[101,104,106] and in some articles this data was not described (probably idiopathic AU patients).[99,103,105,107,109]

AU was treated with different immunomodulatory drugs, including MTX (mean doses from 7.5 to 25 mg/wk),[99,103,109] SSZ (doses from 500 mg to 4 g/d),[11,102,106] AZA 100 mg/d),[105,107] CsA (data regarding doses were not provided)[104] and anti-TNFα drugs, ADA, and golimumab (GLM)[100,101,108,110] following similar doses to those recommended for rheumatologic conditions.

The number of AU flares before and after treatment was the most evaluated outcome along with AU activity and corticosteroids use. However, we found a great variability between studies in the type of outcomes and definitions.

3.1. Methotrexate

In patients with idiopathic AU or associated systemic disease, most of them MTX and biologics naïve, MTX significantly decreased the number of AU flares and activity, and increased the time interval between flares (Tables 2 and 3). MTX doses in these patients ranged from 7.5 to 25 mg/wk and this effect was described in the short and long term. In the subgroup of patients taking systemic corticosteroids at baseline, the dose of these drugs was progressively tapered until discontinuation in many of them.[99,103] One study also depicted the same results regardless of HLA-B27 status (positive or negative).[99] Reported AEs were the same as those previously described for MTX.

3.2. Salazopyrin

SSZ (from 500 mg to 2 g/d for 3 years) was evaluated in a low-quality RCT[11] that revealed a significant reduction in the number of AU flares and an improvement in visual acuity of those patients diagnosed with ankylosing spondylitis (AS)-associated AU. No relevant AEs were recorded. In other observational studies, a decrease of UA flares was also observed, without relevant AEs.[102,106] SSZ has been primarily used in idiopathic and AS/SpA-associated AU.

3.3. Azathioprine

A 3-months RCT published in 1969 compared AZA (100 mg/d) with placebo in 16 patients with AU. The authors did not find differences in visual acuity, number of anterior chamber cells, AU flares, or intraocular pressure after 3 months of treatment.[105] Another prospective study analyzed the effect of AZA in AU patients of whom 24% were refractory to other immunomodulators.[107] AZA significantly improved ocular inflammation and decreased systemic corticosteroids doses. At 6 months and 1 year, 24% and 35% of patients, respectively, showed no ocular activity. AEs were the same as those usually registered for this drug.

3.4. Cyclosporine A

Regarding CsA, in a moderate quality observational study,[104] that included AU patients (almost 75% with a systemic disease-associated AU), 33% by 6 months and 51% by 1 year gained sustained and complete control of inflammation over at least 2 visits spanning at least 28 days. Besides, a steroid-sparing success was achieved by 22.1% by 6 months and 36.1% within 1 year. The most frequent AE in this study was renal toxicity.

3.5. Anti-TNFα agents

We included 3 articles reporting the outcomes of adalimumab (ADA) in AU. All were observational studies in which the majority of participants were SpA-associated AU patients (up to 40% refractory to other anti-TNFα agents). In this population,

Table 1

Excluded articles and reason for exclusion.

No.	Study	Reason for exclusion
1	Abu El-Asrar, 2013	Specific data for AU patients are not shown
2	Akman-Demir, 2008	Specific data for AU patients are not shown
3	Al Rashidi, 2013	Apparently all cases were diagnosed with panuveitis
4	Alpsoy, 2002	Uveitis classification is not clear
5	Androudi, 2003	80% are AU, but there is not a subanalysis of patients with AU
6	Arcinue, 2015	35% are AU, but there is not a subanalysis of patients with AU
7	Arevalo, 2015	Treatment data for AU patients are not shown
8	Aydinoglu-Candan, 2015	Treatment data for AU patients are not shown
9	Barreiro-de-Acosto, 2012	Specific data for AU patients are not shown
10	Baughman, 2005	Specific data for AU patients are not shown
11	Bernauer, 2014	Specific data for AU patients are not shown
12	Biasi, 2000	Specific data for patients with AU are not shown
13	Braun, 2005	Efficacy data for patients with a previous diagnosis of AU are not shown. Analyzes SpA patients treated with anti-TNFα, some of them with AU but not all of them
14	Buggage, 2007	Specific data for AU patients are not shown
15	Calvo-Rio, 2014	Specific data for AU patients are not shown
16	Cervantes-Castaneda, 2009	Specific data for AU patients are not shown
17	Chipont, 1993	AU patients not included
18	Cordero-Coma, 2013	Specific data for AU patients are not shown
19	Cordero-Coma, 2014	Specific data for AU patients are not shown
20	Cuchacovich, 1999	A subanalysis of AU patients was not performed
21	Davatchvi, 2003	AU patients not included
22	De Fidelix, 2015	AU patients not included
23	Demiroglu, 2000	Article rejected by Lancet once published because patients did not sign the informed consent and Ethics Committee did not approve the study
24	Deuter, 2010	AU patients not included
25	Díaz-LLopis, 2008	n=1 AU patient
26	Díaz-LLopis, 2012	A subanalysis of AU patients was not performed
27	Dick, 2013	AU patients are excluded
28	Durrani, 2016	A subanalysis of AU patients was not performed
29	Flores, 2001	A subanalysis of AU patients was not performed
30	Foster, 2003	Uveitis classification is not clear
31	Fujino, 1999	Uveitis classification is not clear
32	Galor, 2008	AU patients not included
33	Galor, 2006	A subanalysis of AU patients was not performed
34	Giardina, 2011	AU patients not included
35	Gueudry, 2008	AU patients not included
36	Guingard, 2006	Uveitis classification is not clear
37	Hasanreisoglu, 2016	Uveitis classification is not clear
38	Hogan, 2007	n=3 AU patients
39	Hueber, 2010	n=5 AU patients
40	Interlandi, 2014	A subanalysis of AU patients was not performed
41	Isnard, 2002	Specific data for AU patients are not shown
42	Joshi, 2014	A subanalysis of AU patients was not performed
43	Jouve, 2016	n=3 AU patients
44	Kaplan-Messas, 2003	Uveitis classification is not clear
45	Kavandi, 2016	All patients were diagnosed with panuveitis
46	Krause, 2008	A subanalysis of AU patients was not performed
47	Kruh, 2014	A subanalysis of AU patients was not performed
48	Larkin, 1999	n=2 AU patients (anterior scleritis)
49	Lau, 2003	A subanalysis of AU patients was not performed
50	Lee, 2012	Specific data for AU patients are not shown
51	Lian, 2015	57.1% were AU but a subanalysis of this group was not performed
52	Martel, 2012	39% of cases are AU but a subanalysis of AU patients was not performed
53	Munoz-Fernandez, 2003 (5	n=9 AU patients
54	Ozyazgan, 1992	No specific data for patients with AU
55	Papaliodis, 2003	Uveitis classification is not clear
56	Prete, 2014	46.1% were AU but a subanalysis of this group was not performed
57	Riancho-Zarrabeitia, 2015	n=3 AU patients
58	Rudwaleit, 2016	Certolizumab was prescribed for SpA. Patients with a previous history of AU are analyzed without mentioning more details about this condition. In the discussion, they comment that ocular flares are AU flares
59	Saenz, 2000	SLR in which articles fulfilling criteria for our SLR are already included
60	Sainz de la Maza, 2012	Specific data for AU patients are not shown
61	Sainz de la Maza, 2016	Specific data for AU patients are not shown
62	Sakai, 2013	Uveitis classification is not clear
63	Shakoor, 2014	The article shows the number of recurrences in patients discontinuing Infliximab. This question does not fit with the purpose of our study
64	Sieper, 2010	Uveitis classification is not clear. AU history is collected indirectly
65	Simonini, 2015	SLR in which articles fulfilling criteria for our SLR are already included
66	Smith, 2001	n=4 AU patients
67	Sobaci, 2010	AU patients not included
68	Sobrin, 2007	n=8 AU patients
69	Sobrin, 2008	Uveitis classification is not clear
70	Suhler, 2005	AU patients not included
71	Suhler, 2013	n=3 AU patients
72	Suhler, 2014	The inclusion of AU patients is not clear
73	Sullu, 1998	Uveitis classification is not clear
74	Takeuchi, 2012	Uveitis classification is not clear
75	Takeuchi, 2013	Labeled as systematic review but not described
76	Takeuchi, 2014	n=4 AU patients
77	Tugal-Tutkun, 2006	Apparently, all cases are posterior uveitis or panuveitis
78	Tugal-Tutkun, 2016	Patients with AU are not included
79	Vallet, 2015	Uveitis classification is not clear
80	Vallet, 2016	15% of cases are AU but a subanalysis of this group was not performed
81	Vitale, 1996	Most of them are intermediate or posterior uveitis
82	Wieringa, 2013	35,9% were AU but a subanalysis of this group was not performed
83	Wu, 2015	Systematic review including clinical trials designed to evaluate efficacy and safety in SpA. Uveitis was subanalyzed, in some cases new episodes. However, in most of them the anatomic classification is not specified, and if done, n is very low
84	Yacizi, 1990	Uveitis classification is not clear
85	Zaghetto, 2010	n=4 AU patients

AU=anterior uveitis; SLR=systematic literature review; SpA=spondyloarthritis; TNF=tumor necrosis factor.

Table 2

Main characteristics of the included studies.

No.	Study	Population	Intervention(s)	Outcomes	Quality/others*
1	Bachta, 2016, observational prospective, mean follow-up 3.3 y, single center	n=19 patients AU (≥3 flares), 68.4% unilat, 57.9% men, mean age 38±14 y, 42% HLA-B27+, 26% systemic corticosteroids IC: immunomodulators naïve EC: SpA features, autoimmune systemic disease, malignancies or other serious diseases, laboratory abnormalities	MTX 15 mg/w po 4 w → 25 mg/w Folic acid 15 mg/w Systemic corticosteroids (tapered until discontinuation) If AU flare topical steroids and mydriatics were used	Δ Flare (n°, patient-y) Time to AU flare % Patients flare-free Time to discontinuation of systemic steroids AE	Oxford 3b Anatomic classification, ocular inflammation or flare not defined
2	Benítez del Castillo, 2000, RCT, duration 3 y, single center	n=22 AS associated AU, 77% men, mean age 36±4 y, 100% HLA-B27+ IC: ≥2 AU flares in the last year, chronic intestinal inflammation	Group 1 (n=10) SSZ 500 mg b.i.d. → daily increase to 3–4 g/d for 6 m → taper to 1 g b.i.d. Group 2 (n=12) no systemic treatment Topical and systemic NSAIDs allowed	N° AU flares (patient-y) Flare severity Blood-aqueous barrier permeability Visual acuity Severe persistent posterior synechiae AE	Jadad 1/Oxford 3b-4 Anatomic classification, ocular inflammation or flare not defined
3	Calvo-Rio, 2016, observational prospective, duration 2 y, multicen	n=15 AS associated AU, 87% men, mean age 39±6 y, 73% HLA-B27+, 47% chronic AU, 53% recurrent, 87% unilat, 67% refractory to ≥ 1 anti-TNFα IC: AU refractory to DMARDs (defined as no clinical remission) EC: Malignancies, systemic infections	GLM 50 mg/m sc DMARDs (n=8) Steroids	Δ Visual acuity (Snellen test) Δ Anterior chamber cells (activity if ≥1 cell) Vitritis (activity if >0) Macular thickness (OCT) Δ N° AU flares Δ Systemic steroids dose % Patients in clinical remission	Oxford 3a IUSG anatomic classification, SUN ocular inflammation
4	Dobner, 2013, observational retrospective, mean follow-up 87 w, multicen	n=60 patients (83% AU, n=21 SpA/AS associated AU, n=5 idiopathic AU, n=4 PsA associated AU, n=1 Behçet), 57% women, mean age 37 y, 42% previous IFX/ETN	ADA 40 mg/2 w sc Systemic steroids allowed	Improvement criteria: ↑ Visual acuity ≥ 2 lines (Snellen Test) ↓ Anterior chamber cells ≥ 2 grades ↓ N° mean AU flares/y ↓ Macular edema (OCT) ↓ Systemic steroids dose <10 mg	Oxford 3a No definition of anatomic classification
5	Dougados, 1993, observational retrospective, mean follow-up 20 y, single center	n=22 SpA associated AU, 59% men, 86% HLA-B27+ IC=SpA, ≥1 AU flare, SSZ for a condition other than AU	SSZ dose 1–3 g/d, most of patients 2–3 g/d, mean follow-up 19 m	Δ N° AU flares (observed by an ophthalmologist, ≥2 d or steroid local injection needed)	Oxford 4 No definition of anatomic classification
6	Gangaputra, 2009, observational retrospective, mean follow-up 0.73 y, multicen	n=126 AU, 71.4% women, mean age 33 y, 65.1% bilateral, 77.8% prednisone ≤10 mg/d, 232 eyes 36.3% visual acuity ≤20/50, 35.2% low activity or active, 6.3% previous MTX, 3.2% other previous immunomodulator, 4.8% previous biologic therapy IC: MTX (monotherapy)	MTX (83% po), maximum dose: ≤12.5 mg/w 48.4% ≥12.5 ≤17.5 mg/w 21.4% ≥17.5 ≤22.5 mg/w 17.5% 22.5 mg/w 12.7% Systemic steroids allowed	Successful treatment (≥2 visits, separated by ≥28 days) Inflammatory control (≥2 visits, separated by ≥28 days) 6 and 12 m (based on clinical history), for patients with low activity or active at baseline: No activity No activity/low activity No activity after ↓ prednisone ≤10 mg/d No activity after ↓ prednisone ≤5 mg/d No systemic steroids ↓ MTX dose after stable maintenance dose for 6 m Steroid-sparing success (inactive inflammation at ≥2	Oxford 2c No definition of anatomic classification Apparently SUN recommendations for classification of ocular inflammation are applied

(*continued*)

Table 2

(continued).

No.	Study	Population	Intervention(s)	Outcomes	Quality/others*
				visits spanning ≥28 days after tapering prednisone to ≤10 mg/d) 6 m after ↓ MTX ↑ MTX dose after stable maintenance dose for 6 m Success in saving steroids (complete inflammatory control ≥2 visits, separated ≥28 days, after ↓ prednisone ≤10 mg/d) after ↑ MTX 6 m Steroid-sparing success at 6 m Steroid-sparing success at 12 m No activity at any visit at 6 m Steroid-sparing success at 6 m at any visit AE	
7	Kacmaz, 2010, observational retrospective, median follow-up 0.9 y, multicen	n=75 AU (133 eyes, 55.6% ≤20/50, 58.6% ocular complications, 58.6% inactive, 20.3% low activity, 20.1% active), 74.7% women, 45.3% ≥40 y, 73.6% bilateral, 73.6% systemic disease associated	CsA monotherapy Systemic steroids allowed	Treatment success (≥2 visits, separated ≥28 days, pat with low activity or active at baseline) 6, 12 m No activity No activity/low activity No activity after ↓ prednisone ≤10 mg/d No activity after ↓ prednisone ≤5 mg/d No activity without systemic steroids No activity at any visit at 6 m No activity after ↓ prednisone ≤10 mg/d ≥1 visit at 6 m AE	Oxford 2c No definition of anatomic classification Apparently SUN recommendations for classification of ocular inflammation are applied
8	Mathews, 1969, RCT double blind, placebo control, duration 3 m, single center	n=16 AU (no more data)	AZA 100 mg/d Placebo Local or systemic steroids and other standard therapies could be maintained/added	Classification: improvement, unchanged, worsening Visual acuity Anterior chamber cells Flares IOP AE	Jadad 3/Oxford 3a No definition of anatomic classification or response criteria
9	Muñoz-Fernandez, 2003, observational prospective, duration 1 y, single center	n=10 AU, 70% women, mean age 47 y, 70% SpA associated, 30% idiopathic, mean previous flares 3,4 IC: ≥3 AU flares previous y, ≥1 flare in the last 3 m EC: infectious uveitis, malignancies, SSZ contraindicated	SSZ 500 mg/d →2 g/d If flare ↑ SSZ 3 g/d Topical treatment if flare No oral steroids or other immunomodulators	Response (↓ n° AU flares) 1 y vs previous y Δ AU flares AE	Oxford 3a Anatomic classification according to IUSG
10	Pasadhika, 2009, observational prospective, duration 1 y, multicen	n=21 AU (35 eyes), 66.7% women, mean age 40 y, 66.7% bilateral, 34.3% active, 23.8% previous immunomodulators, 0% previous biologic therapy	AZA monotherapy Topical treatment and systemic steroids allowed	In patients with activity or mild activity at 6 m and 1 y: % Without inflammation (≥2 visits separated by ≥28 d) % Low inflammation or no inflammation % Without inflammation and prednisone ≤10 mg/d % Without inflammation and prednisone ≤5 mg/d % Without inflammation and prednisone 0 mg/d AE	Oxford 3a No definition of anatomic classification Apparently SUN recommendations for classification of ocular inflammation are applied
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(*continued*)

Table 2

(continued).

No.	Study	Population	Intervention(s)	Outcomes	Quality/others*
	Rudwaleit, 2009, observational prospective, duration 20 w, multicen	n = 274 AS associated AU, 70% men, mean age 45 y, 16% chronic, 10% symptomatic, 91% HLA-B27+, 23% previous IFX and/or ETN	ADA 40 mg/2 w sc 13% SSZ 13% oral steroids	N° AU flares % Patients with AU flare Δ AU flares (100 patients-y, % flare reduction): Whole study group Patients with recent history of AU (≥1 previous flare) Patients with symptomatic AU at the study on-set Patients with previous chronic AU ADA discontinuation	Oxford 2c No definition of anatomic classification Classified in acute or chronic according to SUN recommendations
12	Samason, 2001, observational retrospective, mean follow-up 16 m, single center	n = 104 chronic AU (recurrent or persistent uveitis >3 m)	MTX 7,5 mg/w →↑ up to response or intolerance, or max dose without response Folic acid 1 mg/d Some patients CsA or other concomitant immunomodulators	Control of inflammation (<1 + anterior chamber cells ≥6 consecutive m) AE	Oxford 3a IUSG anatomic classification
13	Yazgan, 2016, observational retrospective, mean follow-up 11 m, single center	n = 12 recurrent SpA associated AU (15 eyes), 100% HLA-B27 +, 58% women, mean age 55 y, 25% bilateral, median previous flare 3 IC: Severe SpA (83% refractory to immunomodulators, 50% to previous biologic therapy) EC: Other concomitant rheumatic diseases	GLM 50 mg/m sc Topical steroids 100% Systemic steroids 50% Subtenonian infiltration 17%	Δ Topical steroids (patients, drops) Δ Systemic steroids (patients, dose) Remission (absence of anterior chamber cells + no flare) New ocular complications Δ N° flares Δ Visual acuity AE	Oxford 3b No definition of anatomic classification Anatomic classification according to IUSG

* Studies quality was assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2011 update (see methods section).

ADA = adalimumab, AE = adverse events, AS = ankylosing spondylitis, AU = anterior uveitis, AZA = azathioprine, CsA = cyclosporine A, d = day, EC = exclusion criteria, ETN = etanercept, GLM = golimumab, g = grams, IC = inclusion criteria, IFX = infliximab, IOP = intraocular pressure, IUSG = International Uveitis Study Group, m = month, max = maximum, mg = milligrams, MTX = methotrexate, multicen = multicentric, NSAIDs = nonsteroidal anti-inflammatory drugs, OCT = optical coherence tomography, pat = patient, po = per ora, PsA = psoriatic arthritis, RCT = randomized controlled trial, sc = subcutaneous, system = systemic: TNF = tumor necrosis factor, SpA = spondyloarthritis, SSZ = salazopyrin, SUN = Standardization of Uveitis Nomenclature, unilat = unilateral, w = week, y = year.

Table 3

Main results of the included studies.

No.	Study	Efficacy	Safety
1	Bachta, 2016	Study population: Δ Total n° AU flares 111 vs 7 ($P < .001$) Δ AU flares 2.12 vs 0.11 patient-y ($P < .001$) Δ Time until AU flare 4.8 vs 18.3 m 84% AU flare-free Systemic corticosteroids withdrawal ~ 3 m after MTX HLA-B27+ patients: Δ Total n° AU flares 42 vs 7 ($P < .001$) Δ AU flares 2.05 vs 0.21 patient-y ($P < .001$) HLA-B27− patients: Δ Total n° of AU flares 69 vs 0 ($P < .001$) Δ AU flares 2.16 vs 0 patient-y ($P < .001$)	n=1 discontinued MTX due to nausea and persistent abdominal pain n=5 patients mild AE (n=3 transient hypertransaminasemia n=2 periodic episodes of nausea, n=1 transient fatigue, n=3 abdominal distension)
2	Benítez del Castillo, 2000	N° AU flares (P=.016): SSZ vs no systemic treatment by 1 y: 0.50±0.53 vs 1.33±1.23 SSZ vs no systemic treatment by 2 y: 0.60±0.84 vs 0.83±0.94 SSZ vs no systemic treatment by 3 y: 0.30±0.67 vs 1±1.04 Mean visual acuity SSZ vs no systemic treatment by 3 y: 0.8 vs 0.6 (P=.050) Severe persistent posterior synechiae (before/end of study): 4/4 in SSZ group vs 4/8 in the no systemic treatment group (P=.65)	No AE
3	Calvo-Rio, 2016	Δ from baseline to 2 y: Mean visual acuity from 0.62±0.3 to 0.84±0.2 Anterior chamber cells median 1 (0–3) to 0 (0–0) (P=.040) OCT from 295±42.2 μm to 259.2±10.3 μm (P=.36) AU flares from 5/y to 0.5/y (0–3.5) (P=.08) Prednisone dose from 4.4±19.4 mg/d to 9.27±0.3 mg/d (P=.040) 87% Patients in clinical remission after a mean follow-up of 23±7 m	n=1 patient with AU flare after 4 m of GLM requiring dose escalation to 100 mg/m n=1 patient without clinical remission n=1 renal adenocarcinoma n=1 mild local injection-site reaction n=1 mild facial herpes zoster
4	Dobner, 2013	SpA/AS associated AU (n=21 patients): n=19 (90.5%) improved ≥1 improvement criteria n=2 (9.5%) worsened ≥1 improvement criteria No efficacy differences between patients previously treated with anti-TNFα vs nontreated with anti-TNFα 5-Idiopatic AU (n=5 patients): n=4 (80%) showed efficacy (data not specify) APs associated AU (n=4 pat): n=3 (75%) showed efficacy (data not specify) Behçet associated AU (n=1 patients): No improvement	No specific safety data for AU patients In the whole study sample n=13 (21.7%) discontinued ADA n=8 inefficacy n=2 hypertransaminasemia n=1 forunculosis n=1 pregnancy n=1 death
5	Dougados, 1993	AU flares without SSZ 29.5 100 patient/y vs 18.4 with SSZ ($P < .010$)	—
6	Gangaputra, 2009	Treatment success at 6 m: No activity 55.6% No activity/slightly active 69.7% No activity after ↓ prednisone ≤10 mg/d 46.1% No activity after ↓ prednisone ≤5 mg/d 41.8% No systemic corticosteroids 6.2%	No specific data for AU In the whole study sample: n=60 (16%) withdrew due to MTX-related AE n=11 (2.9%) GI upset n=6 (1.6%) allergy n=5 (1.3%) mouth ulcers

(*continued*)

Table 3
(continued).

No.	Study	Efficacy	Safety
		↓ MTX dose after stable dose maintained 23.5% Steroid-sparing success after↓ MTX 0% ↑ MTX dose after stable dose maintained during 6 m 46.9% Steroid-sparing success after ↑ MTX 6 m 23.7% Steroid-sparing success at 6 m 46.1% No activity at any visit before 6 m 70.5% Steroid-sparing success at any visit before 6 m 56.4% Treatment success at 12 m: No activity 67.2% No activity/slightly active 71.6% No activity after ↓ prednisone ≤10 mg/d 62.6% No activity after ↓ prednisone ≤5 mg/d 59.4% Without systemic corticosteroids 17.6% Steroid-sparing success at 12 m 62.6%	n=9 (2.3%) hypertransaminasemia n=2 (0.5%) hair loss n=3 (0.8%) infection n=8 (2.1%) malaise n=10 (2.6%) bone marrow suppression n=2 (0.5%) respiratory complaint n=1 (0.3%) cirrhosis n=7 (1.8%) other AEs
7	Kacmaz, 2010	Treatment success at 6 m: No activity 30.4% No activity/slightly active 52.8% No activity after ↓ prednisone ≤10 mg/d 28% No activity after ↓ prednisone ≤5 mg/d 26.9% No activity without systemic steroids 8.8% Treatment success at 12 m: No activity 54.3% No activity/slightly active 85.8% No activity after ↓ prednisone ≤10 mg/d 42.4% No activity after ↓ prednisone ≤5 mg/d 40.4% No activity without systemic corticosteroids 14.9% No activity at any visit before 6 m 56.9% No activity after ↓ prednisone ≤10 mg/d 1≥ visit before 6 m 52.5%	No specific data for AU In the whole study sample: n=43 (11.5%) withdrew due to CsA-related AE. n=12 (3.21%) arterial hypertension n=16 (4.29%) renal toxicity n=3 (0.80%) gingival hyperplasia n=4 (1.07%) hypertransaminasemia n=2 (0.54%) hirsutism n=2 (0.54%) opportunistic infection n=3 (0.80%) malaise n=1 (0.27%) bone marrow suppression n=8 (2.14%) other AEs
8	Mathews, 1969	Improvement, unchanged, worsening at 3 m Visual acuity AZA vs placebo (ns) Anterior chamber cells (ns) Flares (ns) IOP (ns)	n=1 transient neutropenia in AZA group
9	Muñoz-Fernandez, 2003	Response (↓ n° of AU flares) 1 y: 90% Δ AU flares 1 y: 40% (n=2 SpA, n=2 idiopatic) ↓ n° of AU flares, 50% without AU flares	n=2 mild and transitory hypertransaminasemia not requiring SSZ discontinuation
10	Pasadhika, 2009	Control of inflammation (no activity) 6 m: 23.7% Improved inflammation to slightly active or inactive 6 m: 28.2% Control of inflammation and prednisone dose ≤10 mg/d 6 m: 16.6% Control of inflammation and prednisone dose ≤5 mg/d 6 m: 11.5% Control of inflammation and prednisone dose 0 mg/d 6 m: 0% Control of inflammation (no activity) 1 y: 34.6% Improved inflammation to slightly active or inactive 1 y: 42.6% Control of inflammation and prednisone dose ≤10 mg/d 1 y: 24.9%	No specific data for AU In the whole study sample: n=35 (24%) withdrew due to AZA-related AE n=13 (9%) GI upset n=13 (9%) n=7 (5%) bone marrow suppression n=6 (4%) hypertransaminasemia n=3 (2%) infection

(*continued*)

Table 3

(continued).

No.	Study	Efficacy	Safety
		Control of inflammation and prednisone dose ≤5 mg/d 1 y: 19.5% Control of inflammation and prednisone dose 0 mg/d 1 y: 8.3%	n=2 (1%) allergy n=5 (3%) other AEs
11	Rudwaleit, 2009	n=25 AU flares 8.4% patients with AU flare Δ AU flare before vs 1 y of ADA: Whole study sample 68.4 vs 28.9 flares 100 patients-y, 58% reduction ($P <$ .001) Patients with recent history AU 176.9 vs 56 flares 100 patients-y, 68% reduction ($P <$ .001) Patients with baseline symptomatic AU 192.9 vs 96.2 flares 100 patients-y, 50% reduction (P=.001) Patients with chronic AU 129.1 vs 71.4 flares 100 patients-y, 45% reduction (P=.002)	No patient withdrew ADA due to flare n=2 developed new-onset AU (n=1.250 patients)
12	Samson, 2001	Control of inflammation: 81.4%	No specific data for AU In the whole study sample: n=115 (9.2%) withdrew due to ADA-related AE n=8 (5%) hypertransaminasemia n=5 (3.1%) nausea n=4 (2.5%) malaise n=3 (1.9%) leukopenia n=3 (1.9%) artrhalgia n=2 (1.3%) rash n=1 (0.63%) stomatitis n=1 (0.63%) pancreatitis n=1 (0.63%) pneumonitis n=1 (0.63%) neurologic symptoms
13	Yazgan, 2016	Δ Topical steroids 92%, median n° drops 24/d vs 0 mg/d (P=.001) Δ Systemic steroids (n=6), n=4 discontinuation, n=2 ↓ dose, median dose 64 mg/d vs 0 mg/d (P=.027) Remission 67% New ocular complications 0% Δ N° flare 48 vs 1, median 3 vs 0 ($P <$ .001) Δ Visual acuity (n=11 patients) median 0.30 vs 0.09 (P=.002)	n=1 (8%) malignant arterial hypertension

ADA=adalimumab, AE=adverse events, AU=anterior uveitis, AAU=acute anterior uveitis, AZA=azathioprine, CsA=cyclosporine A, d=day, ETN=etanercept, GLM=golimumab, g=grams, IFX=infliximab, IOP=intraocular pressure, m=month, max=maximum, mg=milligrams, MTX=methotrexate, ns=nonsignificant, NSAIDs=nonsteroidal anti-inflammatory drugs, OCT=optical coherence tomography, opth=opthalmologic, po=per oral, sc=subcutaneous, SSZ=sulfasalazine, w=weeks, y=year.

ADA improved different outcomes, including the number of AU flares, ocular inflammation, and dose of corticosteroids. This effect remained in the long term.[101,108,109] One of these studies also showed that the rate of AU flares was reduced by 51% in all study patients, by 58% in 274 patients with a history of AU, by 68% in 106 patients with a recent history of AU, and by 50% in 28 patients with symptomatic AU at baseline. AU flares during ADA treatment in this work were predominantly mild.[108] Expected AE were registered in all studies.

Two more reports analyzing GLM in patients with AU, refractory to immunomodulators including biologic therapies in many patients were included.[100,110] Both studies analyzed a total of 27 patients with SpA-associated AU. The first one depicted a significant improvement in visual acuity, number of UA flares, and need of systemic steroids during a mean follow-up of almost 1 year.[110] On the other hand, 1 patient developed a malignant hypertension and stopped GLM. In the second one, most patients had rapid and progressive improvement in visual acuity and inflammatory parameters as well as in the steroid need. The number of AU flares also decreased but this difference was nonsignificant. In this study, 87% of patients also reached clinical remission after a median follow-up of 23 months.[100]

4. Discussion

We have performed an SLR to analyze the efficacy and safety of immunomodulators when used for treatment of adult patients with noninfectious and nonmalignant AU. To our knowledge, this is the first one specifically designed to analyze patients with AU.

Currently, there is a lack of robust evidence in clinical practice regarding the use of immunomodulators in these patients. Even with this limitation, there is some evidence supporting the use of MTX, SSZ, AZA, CsA, ADA, and GLM.

More specifically, as first line immunomodulators, but also in patients resistant to other immunosuppressive agents, MTX, SSZ, and CsA have shown effectiveness to prevent AU flares, improve visual acuity, and to decrease systemic steroids dose in the short and the long term (up to 3 years). These results have been described in patients with idiopathic AU and patients with an associated systemic disease. In the case of AZA, this drug could also be effective in improving ocular inflammation and in reducing systemic corticosteroids need, in patients who are naïve or refractory to other immunomodulators. This effect has been depicted in the short and long term as well. On the other hand, the evidence also supports the use of ADA and GLM, in different clinical aspects of AU (including refractory patients to other immunomodulators), as they have improved outcomes of interest including AU flares, degree of ocular inflammation, and the need for corticosteroids treatment. In addition, we have evidence of immunomodulators' benefit in the short and the long term. Besides, the AEs reported did not differ from those reported when used these drugs for treatment of other immune-mediated conditions.[111]

As commented before, regarding the study populations, the included studies analyzed patients with idiopathic AU and patients with an associated systemic disease in whom immunomodulators achieved a good response in many of them. In the case of patients with an associated systemic disease, most of them were SpA patients, especially AS, but the studies also included patients with other types of SpA like psoriatic arthritis. Moreover, 1 study found that MTX improved outcomes in both, HLA-B27 positive and negative patients.[99] In this article, although the rate of flares decreased, all the observed flares occurred in the HLA-B27 positive patients.

The selection criteria of the immunomodulators were not described in detail. Classical immunomodulators were used as first-line agents in patients with inadequate response to topical treatments and/or systemic corticosteroids, but also in refractory patients to other immunomodulators, as depicted for anti-TNFα therapies. Doses and routes of administration were those recommended in the summary of products characteristics, and almost 100% of treatments with immunomodulatory drugs were used in monotherapy. Unfortunately there were no comparative studies between immunomodulators.

The main limitation of this SLR is the quality of the included studies that was quite poor in general, limiting the generalization of conclusions. This lack of robust evidence probably, at least in part, might have been solved in daily practice using the evidence and experience from other chronic immune-mediated diseases. Another of the main limitations of the SLR is the lack of proper standardization of the uveitis anatomic classification and definition of outcomes. Therefore, we excluded many articles that actually analyzed patients with AU but did not perform subanalysis of patients with AU. The same way comparisons between studies results were very complicated and a meta-analysis was not possible.

Interestingly, we did not include any article with other biologics like infliximab or tocilizumab. We found some reports during the selection process but eventually excluded them because they did not meet the inclusion criteria, mainly due to lack of subanalysis or due to the sample size of the studies. However, in the literature there are some case series suggesting that these drugs could be effective as those reported with ADA or GLM.[112–114] In the case of etanercept, observational reports have indicated lower effectiveness and some paradoxical occurrence of uveitis following treatment with this agent.[115]

In summary, even with all the limitations exposed previously, immunomodulators could be effective in patients with noninfectious and nonmalignant AU in order to prevent flares and improve other ocular outcomes. However, more research is needed in order to properly define the role of each immunomodulator in this population.

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