ИМУНОМОДУЛИРАЩА ТЕРАПИЯ ПРИ МНОЖЕСТВЕНА СКЛЕРОЗА - АСОЦИИРАН УВЕИТ

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Immunomodulatory therapy in the management of multiple sclerosis-associated uveitis

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Резюме

Цел

Оценка на ефективността на некортикостероидната имуномодулираща терапия за постигане на ремисия или продължителен контрол на възпалителната активност в случаи на увеити, асоциирани с множествена склероза.

Методи

Ретроспективно проучване върху 10 пациенти с увеит и множествена склероза на ,,Massachusetts Eye Research and Surgery Institution''. Преценката за ефективността на терапията се основаваше на контрола на възпалителната активност на увеита.

Резултати

Всички пациенти бяха от женски пол и бяла европеоидна раса и средна възраст 49.3 години. Интермедиерен увеит имаха 6 болни 60%), панувеит – 3 (30%), заден увеит – 1 (10%). Всички случаи бяха двустранни. Имуносупресивната монотерапия беше с метотрексат при 5 пациенти (50%), микофенолат мофетил – при 4 (40%), даклизумаб – при 2 (20%), циклофосфамид – при 2 (20%), метотрексат - при 1 (10%), и циклоспорин - при 1 (10%) пациент. Комбинираната имуномодулация беше с микофенолат мофетил и циклоспорин в 4 случаи (40%), азатиоприн с циклоспорин – в 2 (20%), и метотрексат и циклоспорин – в 1 (10%). Всички пациенти използваха кортикостероиди в периода на проследяването. Седем болни (70%) провеждаха терапия за множествена склероза, от които при 3 (30%) - с глатирамер ацетат, интерферон бета - 1 - а - също при 3 (30%), и интерферон бета -1 -б – при 1 (10%). В края на периода на проследяване при 1 пациент увеитът беше в ремисия след терапия с азатиоприн, а при 5 болни (50%) процесът се контролираше от продължителна терапия с имуносупресори и/или кортикостероиди. При 3 пациенти (30%) се наложи имплантация на вътреочен кортикостероиден имплант.

Заключение

Конвенционалните имуносупресори могат да осигурят продължителен противовъзпалителен контрол при пациенти с множествена склероза - асоцииран увеит. В настоящото проучване специфичните за

множествена склероза имуномодулиращи медикаменти - интерферон бета 1 - алфа и бета и глатирамер ацетат, бяха ефективни за екстраокуларните прояви на заболяването, но не успяхме да демонстрираме категорично благоприятно повлияване на вътреочното възпаление.

Ключови думи: множествена склероза, увеит, имуномодулираща терапия

Abstract

Purpose

To assess the efficacy of immunomodulatory therapy in achieving remission and long-term control of inflammation in patients with multiple sclerosis-associated uveitis.

Methods

We did a retrospective case series study on the clinical records of 10 patients with uveitis and multiple sclerosis, treated at the Massachusetts Eye Research and Surgery Institution. The period of study was from July 2005 until November 2012. The evaluation of effectiveness was based on the control of intraocular inflammation.

Results

All patients were female, white, with mean age 49.3 years. Intermediate uveitis was diagnosed in 6 cases (60%), panuveitis – in 3 (30%), posterior – in 1 (10%). Bilateral involvement was present in all (100%) patients. Immunomodulatory medications as monotherapy included methotrexate - in 5 (50%), mycophenolate mofetil – in 4 (40%), daclizumab – in 2 (20%), cyclophosphamide – in 2 (20%), methotrexate - in 1 (10%), and cyclosporin - in 1 (10%) patient. Combined therapy was used with mycophenolate mofetil and cyclosporin in 4 cases (40%), cyclosporin and azathioprine – in 2 (20%), and methotrexate and cyclosporin – in 1 (10%). Corticosteroids were used by all patients. Seven patients (70%) had systemic therapy for multiple sclerosis with Glatiramer acetate in 3 (30%) of them, interferon beta-1a – in 3 (30%), and interferon beta-1b – in 1 (10%). At the end of follow-up, 1 patient (10%) was in remission for 19 months following azathioprine therapy, 2 (20%) – quiescent with no immunomodulatory therapy or corticosteroids for 6 and 12 months, with no previous stable remission, 1 (10%) – stable on mycophenolate mofetil and cyclosporin for 21 months, 2 (20%) – maintained on immunomodulatory therapy and corticosteroids for 8 and 37 months, 5 eyes of 3 patients – quiescent after fluocinolone acetonide intravitreal implant for as long as 60 months, 3 eyes of 2 patients had signs of active disease.

Conclusions

Non-corticosteroid conventional systemic immunomodulatory medications can maintain long-term control of intraocular inframmation in multiple sclerosis - associated uveitis. The specific multiple sclerosis disease-modifying drugs in our study, which were IFN beta-1b, IFN beta-1a, and glatiramer acetate, were efficacious for the management of the non-ocular manifestations of MS but we could not demonstrate a definitive benefit in the control of ocular inflammation, prevention of complications, and steroid-sparing.

Key words: multiple sclerosis, uveitis, immunomodulatory therapy

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory condition of unknown etiology, characterized by the development of plaques of demyelination in the central nervous system (CNS) [23]. Continued demyelination leads to axonal loss and progression of clinical symptoms.

The mean age of the first MS episode has been shown to be 30 years and observations indicate a predilection for the female gender [26]. Prevalence varies geographically, being rare in equatorial regions and commoner in higher latitudes in either hemisphere.

The etiology of MS is still unclarified. No infectious agent has been demonstrated conclusively thus far; though, viral and bacterial causes have been suspected. Available data indicate a complex interplay between environmental (sunlight exposure, vitamin D) and genetic factors [6,13,23,25,29].

With regard to the occurence and progression of the demyelination in MS, it has been proposed that abnormal T-cell regulation may lead to an autoinflammatory response [38]. Subsets of CD4+ T-cells, namely Th17 cells and regulatory T cells, have been implicated in the autoimmune response in MS. Increased expression of interleukin (IL)-17 has been shown in microarray analysis of serum from MS patients [96], and the development of experimental autoimmune encephalitis, the animal model for MS, was significantly suppressed in IL-17-/- deficient mice [16]. Activated inflammatory cells reach the CNS through postcapillary venules in the settings of increased permeability of the blood-brain barrier and target oligodendrocytes via myelin-related proteins such as myelin basic protein and myelin oligodendrocyte glycoprotein [13]. Resultant axonal damage has been associated with an increased inflammatory response [36].

Myelin is not a normal structural component in the human retina but, nevertheless, inflammation with disruption of the blood-retinal barrier and neuronal and axonal loss have been demonstrated in the setting of multiple sclerosis [8, 10, 32, 33, 34].

The frequency of uveitis in patients with MS varies from 0.4% to 26.9% [1,4,5,9,28]. Any anatomical subtype [14] of uveitis has been observed. It is well known that intraocular inflammation may develop as late as 17 years following the onset of MS [40], therefore the longer the follow-up, the higher the prevalence. Various authors estimate the prevalence of MS in the total uveitic population to be around 1–2% [4,9,19,30] with a higher prevalence in patients with intermediate uveitis, from 7.8% to 14.8% [7,18,27,40]. Rodriguez and Foster have found the the prevalence of MS in patients with uveitis was 1.3%, and 8% in the subgroup of patients with intermediate uveitis [31].

By far, with respect to therapy, multiple classes and ways of application of medications have been employed, to no absolute success. Glucocorticoids, such as systemic prednisone and adrenocorticotropic hormone, may ameliorate many of the symptoms of MS by decreasing inflammation, but they have not been shown to induce remission [2]. Azathioprine, methotrexate, sulfasalazine, and cyclophosphamide have demonstrated variable and moderate efficacy at most [20,22,24,37].

At present, disease-modifying drugs (DMDs) represent the staple for long-term therapy for MS [21]. Interferon therapy (IFN-beta1b and IFN-beta1a) has been demonstrated to reduce by about 30% the rate of relapses in active relapsing-remitting MS and, in addition, reduce lesion accumulation on MRI [11]. In a similar fashion, Glatiramer acetate (GLAT) was noted to cause a 29% reduction in relapse rate over 2 years in relapsing-remitting MS [15]. Monoclonal anti-

bodies have also been increasingly used in the therapy of MS [21]. Addition of daclizumab to interferon therapy has been shown to reduce the occurence of new MRI lesions [39].

In view of the above, no definitive and specific guidelines have been devised for the treatment of uveitis, associated with MS.

Purpose

To assess the efficacy of immunomodulatory therapy in achieving remission and long-term control of inflammation in patients with multiple sclerosis-associated uveitis. Secondly, to evaluate the contribution of MS-specific disease-modifying drugs to the control of inflammation.

Material and Methods

We did a retrospective, observational study on the clinical records of 10 patients with uveitis and multiple sclerosis, treated for uveitis at the Massachusetts Eye Research and Surgery Institution (MERSI). The period of study was from July 2005 until November 2012.

Inclusion criteria included:

1. Definitive diagnosis of multiple sclerosis
2. Definitive association between the uveitic entity and MS
3. Immunomodulatory therapy during the course of treatment
4. Minimal follow-up period of 12 months

Exclusion criteria:

1. Uncertain diagnosis of MS
2. Uveitis of other causes, i.e. infectious/autoimmune, concurrent with MS
3. No immunomodulatory treatment for the MS-associated uveitis
4. Follow-up period less than 12 months

For the accomplishment of the primary purpose, the following objectives were set:

1. Primary objective – corticosteroid-free remission for at least 12 months following remission induction and subsequent discontinuation of uveitis-specific immunomodulatory therapy
2. Secondary objective – corticosteroid-free remission for at least 12 months on continuing uveitis-specific immunomodulatory therapy
3. Tertiary objective – long-term control of inflammation with any therapeutic regimens including corticosteroids

The role of MS disease-modifying drugs was additionally assessed in all patients, in whom their use was documented.

Collected data included demographic characteristics at presentation, duration of uveitis/MS prior to presentation, type of uveitis and activity at presentation, associated ocular conditions at presentation, ocular complications during follow-up, ocular surgical procedures and outcomes, MS-associated non-ocular manifestations, therapy prior to presentation, during the follow-up period and outcomes of therapy, including IMT, MS disease-modifying drugs, corticosteroids, other medications/surgeries, best-corrected visual acuity on initial exam and on the last follow-up.

Clinical assessment was based on a complete ophthalmologic exam (BCVA, intraocular pressure measurement, slit-lamp examination, and dilated fundus exam), and fluorescein angiography to further evaluate changes related to vasculitis. Anterior chamber inflammation was graded according to the classification established by the Standardization of Uveitis Nomenclature, and the National Eye Institute system was used for grading vitreous inflammation.

The change in the grade and degree of intraocular inflammation was used to assess treatment success or failure.

Informed consent was obtained from all participants, as well as an institutional board approval. All the proceedings followed the tenets of the Declaration of Helsinki.

Statistical evaluation was done with descriptive statistical methods.

Results

All patients were female, white-caucasian. The age of presentation at our institution varied from 42 to 59 years. The mean age was 49.3 years. Nine patients (90%) were referred with an already established diagnosis of uveitis, whereas 1 patient (10%) had a new onset uveitis. The duration of intraocular inflammation prior to the initial exam at MERSI ranged from 12 to 25 years. On presentation, MS had been diagnosed in 7 patients (70%), while in 3 (30%) - during our monitoring. MS was diagnosed as relapsing-remitting in all patients. The follow-up period was from 36 to 90 months, mean - 70.4 months [Table 1].

On initial examination, active uveitis was observed in 6 (60%) and quiescent in 4 (40%) patients. Among those, who were quiet on presentation, 1 patient (25%) was on azathioprine (AZA) for 8 months, 1 (25%) - on interferon beta-1a (IFN beta-1a), topical prednisolone acetate 1% and a nonsteroidal antiinflammatory medication (NSAID) for 34 months, 1 (25%) - on IFN beta-1a and an NSAID for 36 months, and 1 (25%) had no recent medication history [Table 1].

Anatomically, intermediate uveitis was diagnosed in 6 cases (60%), panuveitis – in 3 (30%), posterior uveitis – in 1 (10%). Bilateral involvement was present in all (100%) patients [Table 1].

Table 1: Demographic data, type, activity, and therapy of uveitis on the initial exam.

	Patient	Age	Gender	Race	Follow-up (months)	Type of uveitis	Activity	Therapy
1	A	55	F	W	87	Intermediate	inactive	AZA (8 monts)
2	B	59	F	W	90	Intermediate	inactive	IFN-beta-1a/PA/NSAID (34 months)
3	C	47	F	W	86	Posterior	inactive	IFN-beta-1a/NSAID (36 months)
4	D	58	F	W	84	Intermediate	active	N/A
5	E	43	F	W	36	Intermediate	active	N/A
6	F	43	F	W	87	Panuveitis	active	N/A
7	G	47	F	W	78	Intermediate	quiet	N/A
8	H	48	F	W	38	Panuveitis	active	N/A
9	I	42	F	W	59	Panuveitis	active	N/A
10	J	51	F	W	59	Intermediate	active	N/A

Abbreviations: ***AZA – azathioprine; IFN-beta-1a – interferon beta-1 alpha; NSAID – nonsteroidal antiinflammatory drug; PA – prednisolone acetate ophthalmic suspension 1%.***

On presentation, concurrent ocular conditions included history and signs of previous optic neuritis in 5 eyes of 4 patients, 3 of which with signs of optic atrophy. One of the patients had posterior uveitis and 3 (30%)– intermediate. Cataract was noted in 4 eyes of 3 patients, one with panuveitis, and 2 – with intermediate uveitis. Nine eyes of 5 patients, one of whom had posterior uveitis, the other 4 – intermediate, were pseudophakic. Secondary glaucoma was observed in 1 patient with intermediate uveitis and 1 with panuveitis was a glaucoma suspect. Macular edema (ME) was found in 8 eyes of 5 patients, 2 with panuveitis and 3 - with intermediate. Seven eyes of 4 patients were status post pars plana vitrectomy (PPV), 3 with intermediate uveitis and 1 – with panuveitis [Table 2].

Structural and functional ocular complications, noted during the course of the follow-up period, comprised of ME in 6 eyes of 4 patients - 2 with intermediate uveitis, 1 – with posterior uveitis, and 1 – with panuveitis. Epiretinal membrane was observed in 1 patient with intermediate uveitis. Transitory ocular hypertension was documented in 1 patient with panuveitis. One patient with panuveitis was diagnosed with secondary glaucoma, and one case of intermediate uveitis, who already had glaucoma on presentation worsened, necessitating Ahmed valve implantation, which was successful. Cataract developed in 5 eyes of 3 patients, 2 with panuveitis and 1 with intermediate uveitis. Progression of previously diagnosed cataract was noted in 4 eyes of 3 patients. Overall, 6 eyes of 5 patients underwent uncomplicated cataract extraction and secondary intraocular lens implantation. Two patients with ME had bilateral intravitreal bevacizumab injections, one of them twice. One of those had an intraviteral triamcinolone acetonide injection. Intravitreal injections were not associated with exacerbation of inflammation. One patient with intermediate uveitis had a PPV with endolaser for a retinal tear, which was uneventful [Table 2].

During the follow-up period, different medications were used in each patient at different points in time. Immunomodulatory medications (IMT) as monotherapy included azathioprine in 1 patient (10%), methotrexate - in 5 (50%), mycophenolate mofetil – in 4 (40%), cyclosporin – in 1 (10%), daclizumab – in 2 (20%), and cyclophosphamide – in 2 (20%). Combined therapy was used with mycophenolate mofetil and cyclosporin in 4 cases (40%), cyclosporin and azathioprine – in 2 (20%), and methotrexate and cyclosporin – in 1 (10%). Corticosteroids by various routes were utilized in all patients (100%). Six patients (60%) were corticosteroid-dependent at the end of follow-up.

Seven patients (70%) had systemic therapy specific for MS. Glatiramer acetate was used in 3 (30%) of them, interferon beta-1a – in 4 (40%), and interferon beta-1b – in 1 (10%).

Individual patient data, comprising uveitis subtype, type, duration and outcomes of therapy are listed below in Table 3:

Our primary objective of a state of remission for at least 12 months without immunomodulatory therapy for the ocular disease, nor corticosteroid use, was achieved by 3 patients (30%). Among them, at the end of follow-up, 1 patient (10%), "A", with intermediate uveitis was in remission for 19 months following AZA monotherapy and no corticosteroids for at least 24 months. She was still continuing on glatiramer acetate (GLAT), peroral diflunisal and topical bromfenac sodium. Duration of AZA therapy was 58 months and that of GLAT – 43 months. During the course of her ocular disease, she had had 5 relapses of inflammation, managed by corticosteroids, reactivation of ME in one eye, and cataract extraction in one eye.

Table 2. Concurrent ocular conditions, complications, and surgery on presentation and follow-up

	Patient	Age	Gender	Race	Type of uveitis	Complications/surgical history on 1st exam	Complications on follow-up	Surgery on follow-up
1	A	55	F	W	Intermediate	Cataract OS Optic atrophy OU Secondary glaucoma OS	ME OS	CE/IOL OS
2	B	59	F	W	Intermediate	Optic atrophy OU Pseudophakia OU Status post PPV OU	none	none
3	C	47	F	W	Posterior	Pseudophakia OU Optic neuropathy OU	ME OD	none
4	D	58	F	W	Intermediate	ME OU Pseudophakia OU Secondary glaucoma OU Status post PPV OU	none	ivt. BV OU Ahmed valve OD
5	E	43	F	W	Intermediate	ME OU Pseudophakia OU	none	ivt. BV OU (twice) ivt. and transseptal TAC
6	F	43	F	W	Panuveitis	Cataract OU ME OU Status post PPV OU	Secondary glaucoma OD	CE/IOL OU
7	G	47	F	W	Intermediate	Cataract OS Optic atrophy OS Pseudophakia OD Status post PPV OS	ME OU	CE/IOL OS
8	H	48	F	W	Panuveitis	ME OD	Cataract OU Secondary glaucoma OD	CE/IOL OD ivt. TAC OD
9	I	42	F	W	Panuveitis	Glaucoma suspect OU	Cataract OU ME OU	Diagnostic PPV OD Transseptal TAC
10	J	51	F	W	Intermediate	ME OD Retinal tear OD	Cataract OD	PPV/EL OD CE/IOL OD Transseptal TAC OD, twice

Abbreviations: ***BV – bevacizumab; CE – cataract extraction,; EL – endolaser; ivt – intravitreal; ME – macular edema; PPV – pars plana vitrectomy;TAC – triamcinolone.***

Table 3. Therapy of MS-associated uveitis

	Patient	Type of uveitis	Activity on last follow-up	Therapy on last follow-up	IMT history	MS-specific drugs
1	A	Intermediate	inactive	GLAT, diflunisal, bromfenac (19m)	AZA (58m)	GLAT
2	B	Intermediate	inactive	CSA, PA, IFN beta-1a (8m)	CSA (55m)	IFN beta-1a
3	C	Posterior	inactive	MMF, CSA, IFN beta-1a, topical flurbiprofen (21m)	MTX (7m) MMF (12m) MMF/CSA (21m)	IFN beta-1a
4	D	Intermediate	inactive	IVFA OU, IFN beta-1a (25m)	DAC (11m) CSA/AZA (1m) i.v. CTX (7m)	IFN beta-1a
5	E	Intermediate	inactive OD active OS	IVFA OD (29m), GLAT	MMF/CSA (2m) CSA/AZA (24m) i.v. CTX (6m)	GLAT
6	F	Panuveitis	inactive	IVFA OU, celecoxib (60m)	MMF (2m) MMF/CSA (1m) DAC (11m)	none
7	G	Intermediate	inactive	no medications (12m)	MMF/CSA (16m) MMF (15m) MTX	none
8	H	Panuveitis	active	GLAT	MTX (12m) MTX/CSA (4m)	GLAT
9	I	Panuveitis	inactive	MTX, corticosteroids (37m), IFN beta 1b	MTX (6m) MMF (1m) MTX (37m)	IFN beta-1b
10	J	Intermediate	inactive	IFN beta-1a, NSAID (24m)	MTX (10m)	IFN beta-1a

Abbreviations: ***AZA – azathioprine; CSA – ciclosporin A; CTX – cyclophosphamide; DAC – daclizumab; IFN – interferon; IVFA – intravitreal fluocinolone acetonide; GLAT – glatiramer acetate; MMF – mycophenolate mofetil; MTX – methotrexate; PA – prednisolone acetate ophthalmic suspension 1%.***

One patient (10%), "G", with intermediate uveitis was quiescent for 12 months without any medications for her eyes or general MS condition. Prior therapy had been with mycophenolate mofetyl (MMF) and cyclosporine (CSA) combination for 16 months and MMF monotherapy for 15 months, and also intravenous methotrexate (MTX). She had had 2 flares of inflammation and ME in both eyes, and had a cataract extraction in one eye. Corticosteroids had been used by topical and intravenous route. Another patient (10%), "J", with intermediate uveitis, following a 10-month course of MTX with concurrent corticosteroid use, had been later stable for 26 months on IFN beta-1a and an NSAID only, before she had another flare-up, adressed by intravenous methylprednisolone infusion. Further, patient had cataract extraction in one eye and PPV with endolaser for retinal tear in the same eye.

The secondary objective of remission, maintained with IMT, without concurrent corticosteroid use for at least 12 months, was accomplished in 1 (10%) patient with posterior uveitis. At the end of follow-up, patient "C" was in a 21-month corticosteroid-free remission on a combination of MMF, CSA, and topical flurbiprofen for the ocular disease, and IFN beta-1a for MS. She had previously failed peroral MTX due to side effects (7 months) and MMF monotherapy (12 months), secondary to active inflammation. IFN beta-1a had been used for 86 months. Complications included ME in one eye.

The tertiary objective of long-term control of inflammation by "any reasonable means", considering the inherent progressive nature of MS, was met by 5 patients, 9 eyes in total (45%). One patient (10%), "B", with intermediate uveitis was quiescent for 8 months on a combination of CSA, topical prednisolone acetate 1% and IFN beta-1a. Duration of CSA therapy was 55 months and that of IFN beta-1a – 90 months. Corticosteroids were used throughout the follow-up period. One patient (10%), "I", with panuveitis in both eyes had been quiet on peroral MTX and peroral/topical corticosteroids, for 37 months.The same patient, 8 weeks following institution of IFN beta-1b had a coincident recurrence of ME in one eye without definitive signs of uveitic inflammation. Also, she had previously failed one month course of MMF. Disease course had been complicated by bilateral cataract and ME. Patient had undergone a diagnostic PPV, which was associated with 4 months of inflammation quiescence. Three patients (30%) with recalcitrant uveitis had a fluocinolone acetonide intraviteral implant (IVFA). Out of them, one patient (10%), "D", with intermediate uveitis was quiescent for 25 months following bilateral implantation and concurrent IFN beta-1a. She had previously failed daclizumab (DAC) due to inadequate control of inflammation (11 months of therapy), CSA and AZA combination (1 month), and intravenous cyclophosphamide (CTX) (7 months). She had an exacerbation of ME in both eyes which was followed by bilateral bevacizumab injections, and worsening of glaucoma in one eye with subsequent Ahmed valve implantation. Another patient (10%), "F", with bilateral panuveitis had inactive inflammation for 60 months after bilateral IVFA and long-term systemic celecoxib use. Prior to that, she had not responded to MMF monotherapy (2 months), addition of CSA (side effects), and DAC (11 months). She had transitory ocular hypertension and progression of cataracs in both eyes with subsequent successful cataract surgery. One patient (10%), "E", with intermediate uveitis had excellent control of inflammation in one eye following an IVFA for 29 months and active inflammation in the other eye. Twenty-one months of GLAT therapy in the given patient did not lead to improvement of ocular inflammation.

At the time of the last follow-up exam, 3 eyes of 2 patients had signs of active inflammation. One of them, patient "H", with bilateral panu-

veitis, was on GLAT, with a duration of therapy 12 months, and topical prednisolone acetate. She had failed peroral MTX monotherapy (12 months) and a combination of MTX and CSA (4 months). Intravitreal triamcinolone acetonide had also been employed once in one eye. Ocular complications included bilateral cataract and secondary glaucoma in one eye. Cataract surgery to the eye with glaucoma was uneventful and improved visual acuity. The other patient, "E" with active intermediate uveitis in one eye had been on GLAT for 21 months and had also failed to respond to combinations of MMF and CSA (2 months), CSA and AZA (24 months), and intravenous CTX (6 months). Further, she had had intravitreal bevacizumab injections and periocular and intraocular triamcinolone to both eyes. Epiretinal membrane formation in both eyes was noted during follow-up.

With respect to non-ocular manifestations of MS, three patients (30%) had no associated complaints during follow-up. Two of them (20%) had been on IFN beta-1a since the onset of follow-up, whereas one (10%) was on GLAT for 43 months. Moreover, 3 patients (30%) had sensory disturbance, 3 (30%) - pain in various loci, 2 (20%) - psychiatric and cognitive disturbance, 1 (10%) - blurry vision due to optic neuritis, and 1 (10%) - diplopia. All of the above were not directly associated with episodes of active ocular inflammation and most, including the optic neuritis and the diplopia, resolved following institution of MS-specific disease-modifying agents.

Discussion

In the present retrospective case-series study, we presented the effects of immunomodulatory therapy with mostly conventional "immunosuppresive" medications and MS disease modifying agents, including IFN beta-1a, IFN beta- on the activity of intraocular inflammation.

As mentioned earlier, various classes of drugs have been employed in the therapeutic approach to patients with MS-associated pathology. Studies, evaluating the efficacy of therapeutic modalities for the ocular manifestations of MS in particular, have been scarce in the available literature. Presently, MS-associated uveitis is managed in a similar way to noninfectous idiopathic uveitis of presumed autoimmune etiology. A stepladder approach, beginning with NSAIDs and advancing to IMT with various agent has been recommended as a reasonable treatment strategy [12].

Therapy in our patients was based on the aforementioned stepladder approach. Treatment failure was not infrequent and 60% of patients have failed three different IMT regimens. Nevertheless, three patients (30%) with intermediate uveitis had achieved corticosteroid-free remission of at least 12 months following IMT administration and discontinuation. One of them had used AZA for 53 months, 1 patient had been on MMF and CSA for 16 months and subsequently MMF monotherapy for 15 months, and the third – on peroral MTX and CSA for 10 months. Corticosteroid-free remission for at least 12 months while on IMT was achieved in one patient with posterior uveitis, who was in a 21-month remission on a combination of MMF, CSA, and topical flurbiprofen.

Long-term control of inflammation without reaching corticosteroid-free state was achieved in 9 eyes of 5 patients. One patient with panuveitis in both eyes had been quiet on peroral MTX and peroral/topical corticosteroids for 37 months. A patient with intermediate uveitis was quiescent for 8 months on a combination of CSA and topical prednisolone acetate 1% . Three patients with recalcitrant uveitis had a fluocinolone acetonide intraviteral implant and had been quiescent for 25 (two eyes), 60 (two eyes), and 29 months (one eye) months.

At the last follow-up exam, 3 eyes of 2 patients had signs of active inflammation. One of

them, with bilateral panuveitis, was on GLAT, with a duration of therapy 12 months, and topical prednisolone acetate. She had previously failed peroral MTX monotherapy for 12 months, and a combination of MTX and CSA for 4 months. Intravitreal triamcinolone acetonide had also been done to one eye. The other patient had intermediate uveitis, active in one eye, and she had been on GLAT for 21 months and had also failed to respond to combinations of MMF and CSA for 2 months, CSA and AZA for 24 months, and intravenous cyclophosphamide for 6 months.

The role of the MS disease-modifying medications in the induction of remission and maintaining control of inflammation was controversial. Glatiramer acetate and IFN beta-1a had been used for 43 and 26 months, respectively, in the therapeutic regimen in two of the three patients who had an IMT and corticosteroid-free remission period of at least 12 months. Interferon beta-1a was also used for 86 months in a patient stable on IMT for at 21 months. A stable patient with a bilateral fluocinolone acetonide implant was also on interferon beta-1a. Interferon beta-1b in a different patient did not prevent development of macular edema in the setting of presumably quiescent inflammation. The two patients, active on the most recent follow-up exam, had been on GLAT for 12 and 21 months respectively, without apparent benefit of this medication on control of inflammation and relapse rate.

Becker, Heiligenhaus and al., had previously demonstrated a beneficial effect of IFN beta-1a on MS-associated uveitis in a non-randomised, retrospective observational case series in 2005. Their study comprised of 24 eyes of 13 patients with a mean duration of treatment 24.6 month. Improvement of visual acuity was noted in 17 eyes, decrease in inflammation in all eyes, and a resolution of ME in 9 out of 13 eyes with this complication [3].

From our results we could not determine with certainty whether IFN beta-1a had any beneficial effect on intraocular inflammation. Besides, a patient on IFN beta-1a still had to receive an IVFA implant. On the other hand, glatiramer acetate, despite showing some promising results in animal studies for treating allergic encephalomyelitis [35], was apparently ineffectual for managing uveitis in our group of patients. Nevertheless, MS disease-modifying drugs, were effective in addressing the non-ocular manifestations of MS that we encountered.

Conclusion

Uveitis, associated with multiple sclerosis, is characterized by a protracted and complicated clinical course. Non-corticosteroid conventional systemic immunomodulatory medications can induce and maintain corticosteroid-free remission. In the event of systemic therapy failure, the intravitreal fluocinolone acetonide implant may present an alternative in recalcitrant cases, considering all the possible complications from the implant itself.

The specific multiple sclerosis disease-modifying drugs in our study, which were IFN beta-1b, IFN beta-1a, and glatiramer acetate, were efficacious for the management of the non-ocular manifestations of MS but we could not demonstrate a definitive benefit in the control of ocular inflammation, prevention of complications, and steroid-sparing.

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