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Induction of durable remission in ocular inflammatory diseases

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PURPOSE. *To describe a paradigm of care for patients with ocular inflammatory diseases aimed at induction of durable remission.*
METHODS. *Retrospective cohort study. The records of 399 patients with ocular inflammatory diseases treated with systemic immunomodulatory therapy (IMT) at the Massachusetts Eye Research and Surgery Institution were reviewed. Durable remission was defined as control of inflammation in the absence of systemic IMT for at least 1 year. Fifty patients met the inclusion criteria.*
RESULTS. *Mean age was 46±22.5 years (range 18–88). All the patients had corticosteroid therapy and failed this therapy before having IMT. Fifty-two percent of the patients had used methotrexate alone or in combination with other medications. Thirty percent of the patients required at least 2 years of therapy with systemic IMT to obtain durable remission, while 44% required 2 to 5 years of therapy to achieve the same. Twenty percent continued to stay in remission, off immunomodulatory drugs, between 2 and 5 years and 18% were in remission for more than 5 years after therapy discontinuation.*
CONCLUSIONS. *IMT can be sight saving in patients. It can be tapered and discontinued successfully without the return of ocular inflammation. Durable drug-free remission is an achievable goal, and should be pursued by ocular inflammatory disease specialists. (Eur J Ophthalmol 2009; 19: 118-23)*

KEY WORDS. *Durable remission, Induction of remission in uveitis, Remission in uveitis*

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INTRODUCTION

Ocular inflammatory disease (OID) is the third leading cause of preventable blindness in the United States. It is estimated that 2.3 million Americans have ocular inflammation each year (1). OID accounts for 10–15% (2) of the blindness in the United States, and 22% of patients with OID are blind in at least one eye (3). For a disease so crippling, it seems odd that the 50-year-old treatment modality of corticosteroids remains the sole mode of therapy employed in the care of most patients with OID. Despite the advances made in the discovery and development of immunomodulatory therapy (IMT) and the recommendations from a multitude of experts and learned societies for IMT use, a significant proportion of patients with OID continue to be treated with corticosteroid monotherapy, despite the presence of frequent recurrences, occurrence of significant adverse effects, and progressive ocular tissue damage. As a consequence, OID continues to rob many patients of useful vision (4-6).

We analyzed the records of 50 patients with various forms of OID who achieved durable remission after being treated with IMT. These patients were referred to Massachusetts Eye Research and Surgery Institution (MERSI) since they failed to have control of ocular inflammation on chronic corticosteroids or even IMT but at inadequate dose or IMT strategy in the face of constant disease progression. We present this report to illustrate that durable

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drug-free remission is possible and an achievable goal.
In this study, IMT was defined as the use of immunosuppressive drugs other than corticosteroids. These drugs include signal transduction inhibitors, antimetabolites, alkylating agents, and biologic response modifiers.

METHODS

Study design

This retrospective cohort study was approved by the institutional review board of the Massachusetts Eye and Ear Infirmary and waiver of informed consent was granted.

Patient selection

All patients who had IMT and were off medication without ocular inflammation for at least 12 months were included in the study.
Electronic chart review of patients treated at MERSI in Cambridge, Massachusetts, was performed. Out of 399 patients with a diagnosis of OID and who were treated with IMT, 50 patients met the criteria for inclusion in this report, which were history of previous IMT for OID, in remission for at least 1 year off all anti-inflammatory medications. Variables assessed included age, gender, ocular diagnosis, systemic associations, duration of OID, follow-up time, time between diagnosis of OID and IMT implementation, total number of immunomodulatory drugs used, total time on IMT, time off medications, and visual acuity at the last follow-up visit. All these 50 patients failed corticosteroid therapy before having IMT.
Patients or their parents were asked to complete a detailed questionnaire concerning history of the present illness, ocular and medical histories, and an extensive review of systems at the initial visit to MERSI. Etiologic diagnostic studies were performed on the basis of the information gleaned and the findings on ocular examination. Every patient was examined at each visit by the same physician (C.S.F.). Visual acuity testing, tonometry, slit-lamp biomicroscopy, and ophthalmoscopy were performed.
Prior to initiation of IMT, all patients were counseled about the potential side effects to therapy. These included potential oversuppression of the immune system, potential damage to the liver or the kidney, and specific potential side effects associated with the specific class of the immunomodulatory agent used. All patients were examined at 6 weekly visits and hematologic monitoring was performed.

RESULTS

General demographics and ocular diagnoses are summarized in Tables I and II.
Twenty percent of the patients had idiopathic anterior uveitis. IMT characteristics are summarized in Table III. Sixty-eight percent required only one medication and 26% required two medications to control ocular inflammation. Two percent of the patients required three medications and 4% required four medications to achieve inflammation control. The most common route of drug administration was oral. Seven patients received the medications intravenously.

TABLE I - GENDER AND AGE DISTRIBUTION AND DISEASE FOLLOW-UP TIME

Gender	No. (%)	Mean age (SD)	Mean follow-up time, mo (SD)
Male	22 (44)	46 (22.00)	108.26 (66.75)
Female	28 (56)	47 (22.67)	134 (93.60)

TABLE II - OCULAR DIAGNOSES

Ocular diagnosis	No. of patients
Idiopathic anterior uveitis	10
HLA B27–associated uveitis	6
Juvenile idiopathic arthritis iridocyclitis	6
Birdshot chorioretinopathy	4
Ocular cicatricial pemphigoid	4
Idiopathic pars planitis	4
Idiopathic posterior uveitis	3
Idiopathic panuveitis	2
Idiopathic scleritis	2
Adamantiades–Behçet disease	2
Sarcoid panuveitis	2
Sarcoidosis-associated anterior uveitis	1
Herpes simples virus anterior uveitis	1
Idiopathic keratouveitis	1
Serpiginous choroiditis	1
Vogt-Koyanagi-Harada syndrome	1
Total	50

TABLE III - IMMUNOMODULATORY THERAPY (IMT) CHARACTERISTICS

Patient	Previous failed IMT	Final IMT	Disease follow-up, yr	Time before IMT, mo*	IMT time, mo	Side effects
1	–	MTX	3.5	1.1	33.9	Fatigue
2	–	MTX	6.5	36	39.8	Viral respiratory infection
3	–	MTX	8.9	12	84	Fatigue
4	–	MTX	5	5	42	Fatigue
5	–	MTX	15.3	24	152.6	Fatigue
6	–	MTX	5	12	29	Fatigue
7	–	MTX	5.2	3	51	–
8	–	MTX	4	5	43.3	Fatigue
9	–	MTX	8.9	11	69	Fatigue
10	–	MTX	5.5	12	30	Fatigue
11	–	MTX	8	36	24	Fatigue
12	–	MTX	4.7	11.8	19.8	Fatigue
13	–	MTX	26.4	228	29.4	–
14	–	MTX	7.4	12	12	Fatigue
15	–	MTX	8.4	0	36	–
16	–	MTX	16.5	0	24	Fatigue
17	–	MM	15.2	0	182.7	Fatigue
18	–	MM	5.1	41	6.97	Zoster reactivation
19	–	MM	5.9	1	56	Fatigue
20	–	MM	11	100	14.3	–
21	–	MM	12.7	78	57	–
22	–	CSA	18.4	0	48	Hypercholesterolemia
23	–	CSA	16.8	12	178	Hypercholesterolemia
24	–	CSA	5	28	14.8	Gum infection
25	–	CSA	16.6	12	60	Hypertension
26	–	CTX	3.3	10	17.2	Nausea, fatigue
27	–	CTX	5	0	25	Nausea, fatigue
28	–	CTX	30.4	180	12	Nausea, fatigue
29	–	CTX	24.4	1	8	Nausea, fatigue
30	–	AZA	3.8	13	24	Transient leukopenia
31	–	AZA	28.3	12	72	–
32	–	CHBL	3.5	16	12.	–
33	–	CHBL	22	232	6	Transient leukopenia
34	–	CHBL	8.5	35	31	–
35	–	MTX + CSA	10.6	12	60	Transient leukopenia
36	–	MTX + ETP	12.3	27	93	Fatigue
37	–	CSA + MM	8.8	0	75.6	Fatigue
38	–	DAP + IVIG	8.3	10.3	49.6	Headaches
39	MTX	MM	11.5	93.2	37	Transient liver enzymes elevation
40	MTX	MM	5.3	0	55.5	–
41	MTX	MM	4.3	17	18	Fatigue
42	MTX	MM	16.5	115	47	–
43	MTX	DZB	8.5	24	66	Skin rash
44	MTX	CTX	5.4	12	45.8	Nausea, fatigue
45	MTX	DZB	5.8	6	48.4	Fatigue
46	MTX	CHBL	5.6	0	66.2	–
47	MTX	CTX	8.2	3	66.9	Transient leukopenia
48	MTX, CTX	DZB	9.9	12	84	Nausea, fatigue
49	MTX, CSA, MM	DZB	3.5	0	25	Fatigue
50	MTX , MM, DZB	INF	20.5	199	11	Transient leukopenia, fatigue, nausea

MTX = methotrexate; MM = mycophenolate mofetil; CSA = cyclosporine; CTX = cyclophosphamide; AZA = azathioprine; CHBL = chlorambucil; ETP = etanercept; DAP = dapsone; IVIG = intravenous immunoglobulin G; DZB = daclizumab; INF = infliximab; * Time between diagnosis and IMT initiation.

Four percent of the patients required systemic corticosteroids concomitantly. One of the patients developed optic disc edema requiring intravenous methylprednisolone and a short course of oral prednisone and another patient required 1 week of oral corticosteroid therapy for control of a uveitic flare.

Thirty percent required at least two years of IMT to obtain drug-free durable remission, and 46% required IMT between 2 and 5 years to eventually achieve drug-free durable remission. Eighteen percent of the patients were on IMT between 5 and 10 years before drug-free durable remission was achieved. Six percent of the patients were on IMT for more than 10 years.

Sixty percent of the patients had been free of inflammation, off medications, for 12–24 months at the time of data analysis. Twenty-two percent were in drug-free remission for 2 to 5 years. Eighteen percent had been in remission for more than 5 years at the time of data analysis.

Mean visual acuity was 20/23 in both eyes. Forty-six percent had 20/20 vision in both eyes. Eighty-eight percent had 20/20 in the better seeing eye.

Of 100 eyes, 84% saw 20/40 or better; 10% were between 20/50 and 20/200 and 6% had a visual acuity less than 20/200. Three eyes had no light perception: two eyes with sarcoidosis developed severe optic neuropathy during the course of the disease, resulting in loss of vision, and one eye with ocular cicatricial pemphigoid had severe corneal neovascularization and scarring. Among all diagnoses, pars planitis, juvenile idiopathic arthritis associated uveitis, and idiopathic panuveitis were the ones most often associated with significant visual loss.

DISCUSSION

The history of immunomodulatory therapy for ocular inflammatory disease began in Spain, with a publication by Roda-Perez in 1951, describing the treatment of a patient with progressive steroid resistant uveitis, with nitrogen mustard (7). Several reports followed, with authors describing their experiences with azathioprine (8), cyclophosphamide (9), chlorambucil (10), and other medications (11). Despite these series of publications from Europe and America, few ophthalmologists have followed the lead of this pioneering treatment for ocular inflammatory diseases. There are 10 or fewer centers in America that have devoted resources and personnel for the care of patients with OID, including care through immunomodulatory therapy. Ours is one such center and in this report, we present clear evidence that durable remission can be achieved if a paradigm of corticosteroid-sparing IMT is pursued with diagnostic vigor and therapeutic aggressiveness in the care of patients with chronic OID.

On the basis of Medline searches, we can find no published data regarding this matter. Wallace and associates (12, 13) published preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. According to their consensus, 6 continuous months of inactive disease on medication defined clinical remission on medication, while 12 months of inactive disease off all anti-arthritis and anti-uveitis medications defined clinical remission off medication. The authors noted that the criteria for remission off medication ideally should predict that a patient has ≤20% probability of disease recurrence within the next 5 years. Hence we chose to focus on medication-free remission for our analysis report, and chose the 12 months off medication without flare-ups of inflammation as our inclusion criterion. But we found that 20% of the patients had been in remission for 5 years or more and 12% had been in remission for more than 10 years.

Once remission is achieved it can be durable. Only two patients required systemic corticosteroids for a while concomitant to the immunomodulatory therapy, and these were tapered and stopped. Most of the patients retained good vision; 88% had vision of 20/20 in at least one eye.

These extraordinary outcomes arise from the employment of IMT prior to patient development of irreversible damage to structures critical for good vision, and from our search for effective alternatives if one or another immunomodulatory agent failed to induce remission.

Evidence-based medicine continues to demonstrate that significant numbers of patients with ocular inflammatory disorders eventually are disabled as a consequence of chronic inflammation. This is especially true for patients with uveitis of certain etiologies, including idiopathic and human leukocyte antigen B27–associated uveitis (14), juvenile idiopathic arthritis–associated uveitis (15), birdshot retinochoroidopathy (16), pars planitis (17), Adamantiades-Behçet disease (18), sarcoidosis (19), serpiginous choroiditis (20-22), and Vogt-Koyanagi-Harada disease (23, 24). We have previously reported that the active, sometimes stubborn and steroid dependent nature of each of these disorders can

be effectively controlled with steroid sparing immunomodulatory agents (25). Others have done so as well (26-28), and so the matter of safety and efficacy of IMT for OID is settled to the point representing the standard of care recommended by the American Uveitis Society and by the International Uveitis Study Group (29). We show that such therapy need not be endless, but rather, that uveitis is curable and chronic, and open-ended therapy can be avoided. Medication-free durable remission is therefore a realistic goal.

In summary, we show that remission is possible through a paradigm of steroid-sparing immunomodulatory therapy and remission can eventually be durable and drug-free. This, then, is our goal, since OID has such an enormous impact on quality of life, yet endless medication use and physician monitoring is also not ideal. Our hope is that this report will stimulate increasing numbers of ophthalmologists to seriously consider this therapeutic intervention in the 21st century.

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