Literature systematic review on the ophthalmological side effects of interferons

Revisão sistemática da literatura sobre os efeitos adversos oftalmológicos dos interferons

YARA DADALI FRAGOSI1, MARINA SANCHEZ SAHM PAGGIARO2, ROBERTA MASTROMAUR02, GABRIELA DA SILVA JACONDINO2, HEATHER MARION WILSON3

ABSTRACT
Interferons alpha and beta have been used worldwide for a few decades, altering the natural history of several severe diseases including hepatitis C, cancer and immune-mediated conditions such as multiple sclerosis. The adverse events profile of interferons is well established, but only isolated reports of ophthalmological complications of interferon therapy have been published. The objective of this study was to carry out a literature systematic review on the subject, bringing to light the need for careful ophthalmological monitoring of patients undergoing interferon treatment. Nearly 500 cases of ophthalmological complications related to interferon have been reported. The most frequent findings were soft exudates, hemorrhages and retina ischemia.

Keywords: Eye; Retina; Interferon alpha/adverse effects; Interferon beta/adverse effects

BACKGROUND
Interferons are natural glycoproteins that have antiviral, anti-proliferative and immune regulatory functions. There are several classes including interferon alpha, beta and gamma. Interferons alpha and beta are used worldwide in the treatment of several diseases including hepatitis C, cancer and immune-mediated conditions such as multiple sclerosis. Due to the long-term use of interferons for most patients, the safety profile of these compounds is well known. Cutaneous(10), hematological(11), psychiatric(12,13), endocrine(14) and hepatic(15) side effects of interferons have been reported. However, some side effects are specifically related to the eye, and a variety of ophthalmological diseases may arise from the use of interferons. Although recognised as relatively rare, ophthalmological complications due to interferons should be considered even if the patient is visually asymptomatic.

The literature on the subject is restricted to case reports or a small series of cases. In order to better understand the most frequent ophthalmological side effects of interferons and the outcome of these conditions, a literature systematic review was carried out.

METHODS
The present study was registered at the Investigational Review Board/Ethics Committee of Universidade Metropolitana de Santos, which waived the requirement for consent from participants, considering only previously published data were used. The PRISMA protocol(16) was employed in order to guarantee the quality of the search and reporting.

Using the PICO framework(8), the authors independently searched for the terms “interferon” OR “interferon alpha” OR “interferon beta” AND “ophthalmology” OR “eye” AND “side effects” OR “adverse events” OR “adverse effects” in the following databases: Medline, Pubmed, Scopus, Index Medicus, Biomed Central, Ebsco Fulltext, LILACS, Scielo and the Cochrane Database of Systematic Reviews, up to December 2010. Abstracts of articles in any language containing these words in English (in the title, key words or abstract) were independently reviewed by the authors. Any differences in views were discussed and settled in a meeting between the authors.

Only published case reports (or case series) regarding human beings were included in the present review. Editorials, abstracts from scientific meetings, animal studies, expert opinions and duplicate reports were discarded.

Every effort was made to obtain the full text of all relevant papers, including contact with authors, editors of journals, and interlibrary loan. These articles were individually read by all of the authors, who summarized the results in an Excel™ file.

The qualitative characteristics of the present study did not foresee publication biases or treatment effects. Likewise, the exclusive data from case reports in the present study did not provide any

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1 Physician, Department of Neurology, Universidade Metropolitana de Santos - UNIMES - Santos (SP), Brazil.
2 Students, Medical Faculty, Universidade Metropolitana de Santos - UNIMES - Santos (SP), Brazil.
3 Dentistry, University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen (UK).

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Correspondence address: Yara Dadalci Fragoso, Department of Neurology, Medical School, UNIMES, Rua da Constituição 374, Santos (SP) - 11015-470 - Brazil - E-mail: yara@bsnet.com.br
evidence for meta-analysis or statistical evaluation. The results were collected mainly for presentation of a summary table with the most frequently reported findings.

RESULTS

A search of published literature containing the terms outlined in “Methods” resulted in retrieval of 551 articles.

From these initial 551 papers, 457 were discarded due to a failure to meet the established inclusion criteria. Four papers could not be retrieved despite all efforts from the authors of the present study.[9-12] These journals had ceased publication or changed name and/or publisher, while attempts to contact the authors directly were not successful. From the abstract contents, it appeared that only two of these papers reported on cases[9-10], while two others reviewed the subject without adding further cases[11,12].

The present study analyzed data from 88 papers on the subject, describing ophthalmological complications of interferon alpha and beta, published between 1993 and 2010[13-101].

The main findings from all 88 papers are summarized in table 1.

INTERFERON ALPHA

There were 471 reported cases of ophthalmological complications related to the use of interferon alpha[13-91]. Some series also included control subjects (n=829) for normalization of the period of use and the dose of interferon alpha for similar populations. Only one paper presented three cases of children with ophthalmological complications due to interferon alpha treatment[85], all other papers reported on adults.

From the 471 reported cases, 66.7% were in males and 33.3% were in females (although not all papers specified the patient gender). The average age was 46.3 ± 10.0 years (9 to 71 years). Twenty patients had been prescribed interferon alpha due to malignancies, while all the others (n=449) were undergoing treatment for hepatitis B and/or hepatitis C.

Soft retinal exudates were the main finding in 67.0% of these patients, followed by retinal hemorrhage and/or severe ischemia in 56.0% of them. The common denominator in all cases was decreased visual acuity as the patient’s main complaint, although there were reports of virtually asymptomatic patients.

Associated retinal microaneurisms, diplopia, visual field defects, papillary edema, uveitis, thinning of nerve fiber layer, ocular myasthenia and/or oculomotor nerve paralysis, panophthalmitis, periphlebitis and unspecific retinal alterations were also reported in more than half of all cases.

A few cases of Vogt-Koyanagi-Harada disease have been described in association with hepatitis C and interferon alpha plus ribavirin. Only cases with very clear relation between the drug and the side effect were included in the review.

The average time for the patient to develop visual symptoms was 21.9 ± 18.1 weeks from onset of interferon-alpha use. Only two case reports presented findings of patients with ophthalmological complications after one year of treatment.

INTERFERON BETA

There were 14 reported cases in ten papers relating ophthalmological complications due to the interferon beta use[92-101]. These patients consisted of three men and eleven women, with an average age of 37.0 ± 13.1 years (20 to 58 years). Eleven of these patients were prescribed interferon beta due to multiple sclerosis, one patient used interferon beta due to hepatitis C, and there was no clear diagnosis for the two remaining patients.

The average time for presenting decreased visual acuity and/or blurred vision was 21 weeks. However, two cases were not included in this calculation, since symptoms and retinopathy developed after several years of interferon beta treatment. These cases were in complete contrast to all the other cases of retinopathy due to interferon treatment.

All patients using interferon beta who have been reported as having ophthalmological complications of the treatment (n=14) presented soft retinal exudates. In addition, two patients also pre-

### Table 1. Summarized data on the main findings reported in the literature, regarding the association of interferon treatment and ophthalmological complications

<table>
<thead>
<tr>
<th>Soft exudates</th>
<th>Hemorrhage</th>
<th>Ischemia</th>
<th>Others</th>
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sented retinal bleeding, one patient presented retinal infarction and one patient presented several vascular micro-occlusions.

**DISCUSSION**

The present study showed that the main ophthalmological complication from interferon treatment is essentially a vascular retinopathy (exudates, ischemia, and hemorrhages). This condition is not difficult to diagnosis in daily practice and should be routinely investigated in patients undergoing interferon alpha or beta treatment. The present systematic review did not identify reports on other ophthalmological complications (affecting ocular surface, ocular adnexa, lens or other tissue), and all interferon-related adverse events seem to be related to the retina and the optic nerve.

It has been highlighted by some authors that particular risk factors may be involved in the development of ophthalmological complications during the use of interferon. Hayasaka et al. reviewed the subject in 1998 and concluded that systemic hypertension and diabetes mellitus were clear risk factors for eye disease during therapy with interferons. Chisholm et al. have reviewed the subject of asymptomatic ophthalmological disease in patients using interferon alpha. Although this was not the subject of the present review (which concentrated in symptomatic patients), the subject deserves attention. It is also important to consider that the association of interferons to other drugs, such as ribavirin, may favor the development of ophthalmological complications. Although most papers reviewed in the present work consider this possibility, it seems that only high blood pressure and diabetes are categorically considered severe risk factors of eye disease during the use of interferons.

Over the last two decades, treatment with interferons has become a common worldwide option for a variety of diseases. Most often, this treatment is used for long periods of time and monitoring of side effects is recommended. Cutaneous, hematological, psychiatric, endocrine and hepatic monitoring is well established by guidelines and clearly explained in leaflets accompanying the medication. On the other hand, ophthalmological side effects of interferons are not well known and there are no guidelines or recommendations for monitoring patients through regular ophthalmological consultations. Popular drug information websites both in English (www.medicinenet.com) and in Portuguese (www.bulasmed.br) do not have specific recommendations for ophthalmological assessments of patients using interferons. The website www.drugs.com recommends consultations in cases of blurred or double vision, but does not suggest regular consultations to detect possible alterations prior to symptoms.

The mechanism of damage to the eye caused by interferon is not completely understood. It is possible that the frequent exposure to interferon induces the production of autoantibodies leading to the deposition of immune complexes in the retina. It is also plausible that the deposition of inflammatory cytokines in the arterial walls of the retina might be related to the development of ophthalmological adverse events.

When a patient presents ophthalmological complications of the interferon treatment, the recommendation is to stop the treatment with interferon. Although many cases reported in the literature showed good outcomes when the interferon treatment was withdrawn, this was not observed in all patients. Especially for cases with vascular damage, the general outcome was incomplete recovery.

There are very few papers reporting on the prevalence of visual adverse events in a population of patients using interferons. One of these papers reports that, of all the interferon-related adverse events, 8.4% affected the eye. In contrast, Cuthbertson et al. analyzing their series of cases did not see any reason to recommend routine ophthalmological evaluation of patients using interferons. The real extent of ophthalmological adverse events caused by interferons may be unknown, since ophthalmological investigation of these patients appears to be performed only when the patients complained of visual symptoms. In addition to the problem, the underlying diseases themselves may also cause visual symptoms. For example, blurred vision could be due to optical neuritis and diplopia may be related to brainstem lesions in multiple sclerosis, and retinal phlebitis have been reported as retinal manifestations of multiple sclerosis, and may add to the difficult differential diagnosis of visual disturbances in a patient with multiple sclerosis who takes interferon. Thus, the physician may consider that the underlying disease is worsening when, in fact, the symptoms could be an adverse effect of treatment. At least for patients at higher risk of developing other concomitant diseases or therapy complications, the association of interferon beta and antiviral therapy should be carefully monitored.

**CONCLUSION**

Although not particularly frequent, ophthalmological adverse events related to the use of interferons have been reported in nearly five hundred individuals over less than three decades. These are patients who already suffer from chronic and debilitating conditions, and poor outcomes of visual affections may play a substantial role in worsening their quality of life. Retinal exudates, ischemia and hemorrhage should be actively investigated in patients undergoing treatment with interferons as part of the extensive monitoring of side effects of these compounds. Therefore, for the first six months of interferon treatment, when most complications have been described, routine ophthalmological assessments could improve the overall quality of care for these patients. If complications are present in a patient taking interferons, the general recommendation is to stop the treatment with this drug.

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