Published in final edited form as:

Lupus. 2010 ; 19(6): 675–682. doi:10.1177/0961203309360539.

Ocular side effects of anti-rheumatic medications: what a rheumatologist should know

V Peponis¹, VC Kyttaris², SE Chalkiadakis¹, S Bonovas³, and NM Sitaras³

¹ Athens Eye Hospital, Second Eye Clinic, Athens, Greece

² Division of Rheumatology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

³ Department of Pharmacology, School of Medicine, University of Athens, Greece

Abstract

Nearly every drug may cause changes to ocular tissues through a variety of mechanisms. Medication overdoses, drug–drug interactions but also chronic administration of medications at the recommended doses may lead to ocular toxicity. The ocular side effects, screening for eye toxicity and treatment guidelines for anti-inflammatory and immunosuppressive drugs commonly used by rheumatologists are reviewed herein.

Keywords

drugs; eye; hydroxychloroquine; lupus

Introduction

The eyes have a relatively small mass and rich blood supply and are therefore highly susceptible to toxic substances. Nearly every drug can cause changes to ocular tissues through a variety of mechanisms such as the production of arachidonic acid derivatives, the liberation of free radicals and the disruption of blood–aqueous and blood–retinal barriers. Medication overdoses, drug–drug interactions but also chronic administration of medications at the recommended doses may lead to ocular toxicity. Recognition of the early signs of eye toxicity, withdrawal of the offending agent and prompt referral to an ophthalmologist may avert permanent ocular damage and vision impairment. Herein we will review the ocular side effects of anti-inflammatory and immunosuppressive drugs commonly used by rheumatologists (Table 1).

Corticosteroids

Corticosteroids bind to the intracellular corticosteroid receptor¹ and thus modify the expression of a variety of genes and alter protein synthesis. Their immunosuppressive effects are mediated via the non-specific suppression of the immune response, making them a mainstay of treatment for a variety of autoimmune disorders.²

The ocular adverse drug reactions (OADRs) of the natural and synthetic steroids are well documented.³ Corticosteroids increase the risk of infection due to immunosuppression and

decreased levels of tear lysozyme and also impaired corneal epithelial wound healing.⁴ The corticosteroids have also been associated with both anterior (subconjunctival hemorrhages, translucent blue sclera, eyelid hyperemia and edema) and posterior (retinal embolic events, central serous choroidopathy⁵) compartment toxicities. Moreover, there have been reports of neurologic adverse drug reactions (ADRs) such as diplopia, nerve palsies, papille-dema and retinal hemorrhages due to intracranial hypertension after epidural steroid injection.^{6–10}

The best documented OADRs from corticosteroid use are the induction of cataracts and the increase of the ocular pressure causing glaucoma.¹¹ In 1960, Black *et al.*¹² were the first to suggest that systemic steroid use could cause posterior subcapsular cataracts (PSC). Steroid-induced PSC are clinically indistinguishable from other forms of PSC, such as the ones found in diabetic patients. The incidence of PSC associated with steroid use increases with increased dosage and duration of treatment, but there is considerable variation in susceptibility between individuals.¹³ Although PSC have been reported to develop after as little as 5 mg of oral prednisone per day for as short as 2 months, the usual time until onset is at least 1 year with doses equal or higher than 10 mg per day of oral prednisone equivalent.^{12,14,15} The incidence of corticosteroid-induced cataracts reported in a number of randomized, controlled trials ranged from 6.4% to 38.7% after oral corticosteroid use.^{16–18}

The pathogenesis of steroid-induced cataract may involve multiple mechanisms. One mechanism that is proposed for the corticosteroid-induced PSC is the formation of covalent adducts of the steroid molecule with the lysine residues of lens particles resulting in lens opacities.^{19,20} Another proposed mechanism is the inhibition of the sodium–potassium pump in the lens epithelium, leading to an accumulation of water within the lens fibres and agglutination of lens proteins.²¹ Other theories postulate that PSC development secondary to corticosteroid use involves elevation of glucose in the plasma and aqueous humor, increased cation permeability, inhibition of glucose-6-phosphate dehydrogenase, inhibition of ribonucleic acid synthesis, and loss of lens ATP. It is therefore plausible that multiple mechanisms are responsible for the development of PSC in patients treated with corticosteroids.²²

Glaucoma secondary to exogenous administration of corticosteroids was documented as early as 1950.²³ Visual field loss, optic disc cupping and optic nerve atrophy with ocular hypertension have been reported as typical signs and symptoms of glaucoma progression.²⁴ Glaucomatous changes were seen in patients taking steroids not only orally or intravenously but also topically, intranasally or via inhalation.^{25–27} The rise in intraocular pressure (IOP) is thought to occur via the accumulation of glycosaminoglycans and water in the trabecular meshwork, reducing aqueous outflow.²⁸ There is also evidence of a genetic etiology for at least some cases of steroid-induced glaucoma. Mutations in the gene encoding for a trabecular meshwork protein (TIGR) that has been mapped on chromosome 1 seem to confer risk for open angle glaucoma in a small subset of patients using steroids.^{29–31}

Armaly³² studied the effect of topical corticosteroids on intra-ocular pressure. He found that 4–6% of clinically healthy people evaluated responded to topical corticosteroids with elevations of IOP greater than 15 mmHg and a total IOP greater than 31 mmHg after daily corticosteroid use for 4–6 weeks; these were deemed high responders. One-third of the population studied were categorized as ‘moderate responders’ after the same treatment, having 6–15 mmHg pressure elevation and an IOP between 20 and 31 mmHg. The remaining two-thirds, the non-responders, had a less than 6 mmHg pressure rise and an IOP of less than 20 mmHg. Groups of patients found to have higher rates of steroid responsiveness included those with open angle glaucoma, diabetes mellitus, high myopia, connective tissue disease (especially rheumatoid arthritis) and those with first-degree relatives with primary open angle glaucoma.^{33–38}

Despite all the published data, we still do not know what is a safe daily dose of corticosteroid and for how long this dose can be maintained. It is difficult to determine a safe steroid dose even by pooling all published data because of the differing diagnostic criteria of the studies as well as the differing potency of steroids used. Patients treated with oral prednisone in amounts less than 10 mg/day for 1 year stand a negligible chance of developing a PSC. However, 75% of patients receiving more than 15 mg/day prednisone for more than one year were found to have cataracts.³⁹

Patients should be advised of the OADRs of these medications and the need for careful monitoring as many of them are asymptomatic. The main OADRs of systemically administered steroids occur with oral use, with little concern with nasal administration, even long term. Topical ophthalmic use, which causes the most significant anterior and IOP-related effects, must be carefully monitored. Timing of follow-up examinations depends on doses and duration of treatment, required every 6 months for cataract formation, but sooner for IOP and retinal/nerve concerns. Those with any visual disturbance must be advised to seek care. Surgical removal of steroid-induced PSC is similar to conventional PSC. IOP elevation is asymptomatic, so it can only be detected with diligent and timely follow-up examinations including applanation tonometry. Steroid-induced IOP elevation typically occurs within 2–6 weeks of beginning steroid therapy. Upon stopping corticosteroids, the IOP usually normalizes in a few weeks to months. For patients on medical therapy alone, the interval of follow-up care is determined by the extent of the IOP elevation and the degree of optic nerve and visual field damage. If IOP is elevated, steroids need to be tapered as much and fast as possible. If unable to lower the steroid dose it is advisable to use antiglaucoma agents to lower the IOP; monitoring should be close with threshold visual fields, stereoscopic examination and photographs of the optic disc and nerve fibre layer imaging according to the American Academy of Ophthalmology.

Non-steroidal anti-inflammatory agents

Non-steroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of agents frequently not related chemically. Nevertheless, they share both therapeutic actions and ADRs. Although these drugs are widely administered and are often used for prolonged periods, ocular side effects are rare and have been poorly described.

Indomethacin is one of the most potent NSAIDs that has been associated with cases of corneal opacities and blurred vision, especially when used long term.⁴⁰ Symptoms associated with the corneal opacities can range from mild light sensitivity to frank photophobia. On slit lamp examination, the corneal lesions appear either as fine stromal speckled opacities or have a whorl-like distribution resembling chloroquine keratopathy. These corneal changes diminish or disappear within 6 months of discontinuing indomethacin.

In addition to keratopathy, cases of retinopathy have been associated with NSAIDs and especially indomethacin.⁴¹ There is evidence that the drug can induce pigmentary changes of the macula and other areas of the retina causing symptoms of blurred vision. The lesions usually consist of discrete pigment scattering of the retinal pigment epithelium (RPE) perifoveally, as well as fine areas of depigmentation around the macula. Depending on the amount of retinal involvement, the electroretinogram (ERG) and electrooculogram (EOG) can be normal or abnormal.⁴² No definite relationship has been established between the dosage of indomethacin and retinal toxicity.

Acetylsalicylic acid (aspirin) is well known to have anticoagulant properties. In high doses or with prolonged use these drugs may increase bleeding tendencies (e.g., subconjunctival

hemorrhage,⁴³ hemorrhagic retinopathy⁴⁴). These agents should be avoided before/after surgery, following trauma and hyphema.

Ibuprofen, Naproxen, Oxaprozin and Piroxicam may also increase bleeding tendencies. Blurred vision, photophobia and central vision changes may occur. Symptoms are generally rare. The association between their use and cases of Stevens–Johnson syndrome is well documented.⁴⁵ This syndrome requires immediate discontinuation of the drug and referral to primary care provider.

Rofecoxib, Celecoxib, Valdecoxib, Lumiracoxib, Nimesulide and Etodolac are NSAIDs selective for the inhibition of cyclo-oxygenase (COX)-2. Conjunctivitis, blurred vision that ranges from spots in vision to temporary blindness is considered an OADR mostly associated with rofecoxib and celecoxib.⁴⁶ Nonetheless, visual symptoms resolve on discontinuation with no long-term effects to the vision.

According to the American Optometric Association (Optometric Clinical Practice Guideline), the initial baseline evaluation should include a comprehensive eye examination, screening of the visual field and color vision testing (blue on yellow). The recommended follow-up interval is an annual comprehensive eye examination, unless ocular signs, symptoms and other clinical findings indicate more frequent periodic care. A central threshold visual field and repeated color vision testing is needed with complaints of visual acuity reduction or in case of color vision changes. Fundus photography should be performed, as indicated.

Sulfasalazine

The reports on ocular side effects from the usage of sulfasalazine are relatively few, despite its commercialization for a long time; the drug is generally considered safe and well tolerated.⁴⁷ There has been a report of peripheral facial nerve palsy and blurred near vision in association with sulphasalazine treatment.⁴⁸ Santodomingo *et al.*⁴⁹ presented a sudden bilateral onset of −1.0 diopters sphere (DS) of myopia in a young adult female following the addition of a sulphonamide (sulphasalazine) to oral non-steroidal anti-inflammatory treatment (meloxicam) for rheumatoid arthritis. The latest report comes from Fuentes *et al.*⁵⁰ who reported a case of a 29-year-old white woman with conjunctival pigmentation after a Stevens–Johnson syndrome episode triggered by sulfasalazine. Stevens–Johnson syndrome may require topical supportive agents, topical and/or oral steroids and antihistamines depending on severity of presentation. Referral to primary care provider and/or dermatologist may be indicated.

Biologics

Biologics are a new class of drugs that recently became available to treat autoimmune diseases. They include the tumor necrosis factor- α inhibitors infliximab, etanercept, and adalimumab; the antilymphocyte drugs rituximab and alemtuzumab; the interleukin-2 receptor blocker daclizumab; and recombinant interferon (IFN)- α .

Abatacept has successfully been used in humans to treat psoriasis, systemic lupus erythematosus (SLE) and rheumatoid arthritis.^{51–53} Its OADRs are generally generic, such as eye irritation, allergic conjunctivitis, blurry vision, visual disturbance and eye pruritus involving less than 1% of the drug users.^{54–57}

Rituximab (RTX) is a human/murine chimeric monoclonal antibody (mAb) that specifically targets the transmembrane protein CD20 on B cells.⁵⁸ A 2005 report on the safety of RTX in patients with cancer and rheumatoid arthritis (RA) concluded that serious adverse reactions

occur only in a small minority of patients but overall RTX therapy is safe.⁵⁹ In a clinical study concerning the efficacy of rituximab in 222 patients with lymphoma, nine of them reported ocular side effects, including conjunctivitis, transient ocular edema, a burning sensation, a transient or permanent, even severe, loss of visual function.⁶⁰

Etanercept and infliximab are tumor necrosis factor- α antagonists used on their own or in combination with other medications to reduce the pain and swelling associated with RA. Reactivation of tuberculosis infection is one adverse effect of their use. Two cases of reactivation of tuberculosis-related chronic granulomatous panuveitis have been reported.^{61,62} There is considerable discussion about whether ocular inflammation is paradoxically a potential adverse event of etanercept in either previously inflamed or uninflamed eyes.⁶³ It is as yet unclear whether etanercept may induce new-onset uveitis or may prevent uveitis. As a result, etanercept should still be considered in treating those with HLA-B27-associated arthropathy without history of uveitis; however, should ocular involvement subsequently occurs, then a switch to either infliximab or adalimumab is warranted.

The IFNs are antiviral glycoproteins naturally produced by most cells in the body in response to a viral infection that modulate the activity of the immunological system. Recombinant IFN- α has been approved for its antiviral effects and the inhibition of cell proliferation. They have been used in neoplastic diseases, hepatitis C and autoimmune diseases (e.g., multiple sclerosis and uveitis), although their mechanism of action in autoimmune diseases is poorly understood. Therapy with IFN- α has been associated with the presence of systemic side effects, such as flu-like syndrome, arthralgia, platelet reduction, leukopenia, depression, delirium, thyroid disorders and ocular side effects.^{64–70} There are descriptions in the literature^{71–84} of retinal vascular abnormalities (retinal microvascular changes, presence of cotton-wool spots, intraretinal hemorrhages, retinal detachment) due to this drug. Mostly, the ocular changes are transient and asymptomatic. However, in some special cases an aggressive intervention should be carried out, such as retinal photocoagulation or surgery.^{85,86} As an initial baseline evaluation during IFN therapy it is recommended a comprehensive eye examination with detailed bio-microscopy, use of Amsler grid, color vision (blue–yellow) testing and fundus photography. The patient should be instructed to use in a weekly basis the Amsler grid at home to detect maculopathy. The recommended follow-up intervals would be every 3 months according to the American Optometric Association.

Anti-metabolites

Methotrexate-related ocular toxicities consist of peri-orbital edema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis, decreased reflex tear secretion⁸⁷ and non-arteritic ischemic optic neuropathy.^{88,89} The optic neuropathy has been linked to folate deficiency, either nutritional or genetic.⁸⁹ Folate supplementation when co-administered with methotrexate, minimizes its adverse effects⁹⁰ and may therefore prevent the development of optic neuropathy. In addition, when this condition is recognized, the nerve damage can be reversed if methotrexate is stopped and appropriate folate supplementation is administered promptly.⁸⁹

A case was reported by Ponjavic *et al.*⁹¹ in which they described a reduced full-field ERG in b-wave amplitude in a 13-year-old boy treated with methotrexate for 8.5 years. Three years after cessation of therapy the multi-focal (mf)ERG demonstrated normal responses in the macular region.

As far as azathioprine is concerned, there is only one case report of ocular toxicity related to its systemic administration. Razonable *et al.* reported a case of secondary infectious uveitis as a consequence of immunosuppression induced by the use of azathioprine.⁹²

Leflunomide is another systemic anti-metabolite used in the therapy of rheumatic diseases. Hassikou *et al.* have only reported a case of reversible ocular mucosal ulcers induced from its application for the therapy of RA.⁹³

Biphosphonates

Biphosphonates are increasingly being prescribed in patients with chronic inflammatory conditions for the prevention and/or treatment of osteoporosis including glucocorticoid-induced osteoporosis.⁹⁴ Several reports have linked the use of biphosphonates to ocular inflammation, in particular uveitis and scleritis.^{95–97} These findings were challenged by a large albeit retrospective study in a veteran population that failed to show a significant increase in uveitis/scleritis in patients prescribed biphosphonates.⁹⁸ Given these data no recommendation can safely be made about the use of biphosphonates in patients with uveitis and/or scleritis. In the absence though of underlying conditions that may have caused the development of inflammatory eye disease, discontinuation of biphosphonate treatment should be considered.

Anti-malarials

Antimalarials have been used to treat lupus since 1894, when Payne used quinine.⁹⁹

Atabrine was developed in Germany during the 1920s and first introduced as an antimalarial therapy in 1930.^{100–102} It has a variety of actions and has been administered to millions of individuals. Its antirheumatic properties have been well documented but have not been exploited optimally for a variety of reasons. The drug is generally quite safe and can be used in low doses in lupus and rheumatoid arthritis patients as a steroid-sparing agent or synergistically with hydroxychloroquine. One of the major advantages of atabrine over the chloroquines is its lack of retinal toxicity. The world's literature contains only one report of 'Atabrine retinotoxicity'.¹⁰³ High doses of Atabrine can rarely induce a hypersensitivity reaction resulting in a reversible corneal edema.^{104,105}

Chloroquine and hydroxychloroquine have been used to treat rheumatoid arthritis, discoid and systemic lupus erythematosus and other collagen and dermatologic diseases since the early 1950s. Initially retinal toxicity due to long-term use of chloroquine (Aralen) for malaria was reported in 1959 by Hobbs *et al.*¹⁰⁶ Currently, hydroxychloroquine sulphate (Plaquenil) is the quinoline agent of choice for the treatment of autoimmune diseases with a far lower incidence of adverse reactions.^{107,108} Hydroxychloroquine has been associated with many ocular toxic effects including keratopathy, ciliary body dysfunction, lens opacities, outer retinal damage, and pigmentary retinopathy. The damage to the retina can lead to visual field defects, decreased visual acuity, colour-vision defects, and abnormalities in ERG and EOG.^{109–111} There are many factors that may contribute to hydroxychloroquine retinopathy. These factors include daily and cumulative dosage, duration of treatment, renal or liver disease, patient's age, and prior retinal disease. Out of these factors, daily dosage is thought to be the most important factor in the development of hydroxychloroquine retinopathy.¹¹⁰ The great majority of case reports of hydroxychloroquine toxicity occurred in individuals taking more than 6.5 mg/kg/day or chloroquine at 3 mg/kg/day, and most of the reports of hydroxychloroquine toxicity at lower doses occurred in individuals who took the drug for at least 5 years.¹¹² Grierson suggests that the risk of toxicity is low if the daily dose is less than 6.5 mg/kg/day and the cumulative dose is less than 200 g. Importantly, at a dose of 400 mg per day, the cumulative dose of 200 g would be reached only after 18 months.¹¹⁷ There are limited data that suggest that patients over the age of 60 years are at higher risk¹¹⁸ and further studies will need to investigate age as a direct factor in hydroxychloroquine toxicity. Shroyer *et al.* have suggested that a mutation of the gene *ABCA4* may increase susceptibility to hydroxychloroquine toxicity.¹¹⁹ While toxicity

reversal is possible when the drug is stopped at a stage of very early functional loss, clinical recovery after the development of bilateral paracentral scotomas or visible bull's eye maculopathy has not been shown to be significant and continued depigmentation with functional loss has been reported.¹²⁰

There is no proven medical therapy for chloroquine or hydroxychloroquine toxicity other than stopping the drug. A decision to stop the drug should be made in consultation with the internist or rheumatologist caring for the patient. The American Academy of Ophthalmology, the Royal College of Ophthalmologists, the American College of Rheumatologists and the Canadian Ophthalmological Society recommended guidelines for monitoring patients on hydroxychloroquine therapy.^{112–116} Suggested at initiation of therapy is a baseline examination consisting of a dilated posterior-segment examination, along with Amsler grid testing or automated perimetry. Baseline fundus photographs and fluorescein angiography (FA) are helpful in patients with pre-existing macular pigmentary changes. The patients should repeat visual acuity testing every six months, screen the visual field, use the Amsler grid and have a detailed funduscopy. Central threshold visual field testing is recommended for suspected optic neuropathy.

Conclusion

Ophthalmic adverse drug reactions are well-documented entities that can complicate systemic antirheumatic therapy. They can involve a specific anatomic chamber of the eye or its totality. It is imperative for the treating clinician to appropriately screen asymptomatic patients and recognise early signs and symptoms of ocular toxicity. Close collaboration between the prescribing rheumatologist and the ophthalmologist will help tailor treatment for patients with drug induced ocular toxicity and avert irreversible eye damage.

Acknowledgments

This work was supported by the National Institute of Arthritis, Musculoskeletal and Skin Diseases Grant K23 AR055672.

References

1. Rousseau GG, Baxter JD, Tomkins GM. Glucocorticoid receptors: relations between steroid binding and biological effects. *J Mol Biol* 1972;67:99–115. [PubMed: 4402888]
2. Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995;332:1351–1362. [PubMed: 7715646]
3. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000;11:478–483. [PubMed: 11141645]
4. Waterbury L, Kunysz EA, Beuerman R. Effects of steroidal and non-steroidal anti-inflammatory agents on corneal wound healing. *J Ocul Pharmacol* 1987;3:43–54. [PubMed: 3503908]
5. Haimovici R, Gragoudas ES, Duker JS, et al. Central serous chorioretinopathy associated with inhaled or intranasal corticosteroids. *Ophthalmology* 1997;104:1653–1660. [PubMed: 9331207]
6. Purdy EP, Ajimal GS. Vision loss after lumbar epidural steroid injection. *Anesth Analg* 1998;86:1191–1122.
7. Victory RA, Hassett P, Morrison G. Transient blindness following epidural analgesia. *Anaesthesia* 1991;46:940–941. [PubMed: 1836315]
8. Ling C, Atkinson PL, Munton C. Bilateral retinal haemorrhages following epidural injection. *Br J Ophthalmol* 1993;77:316–317. [PubMed: 8318472]
9. Cousins, MJ.; Bridenbaugh, PO. Neural blockade in clinical anesthesia and management of pain. 2. Lippincott, JB., editor. 1988. p. 946-950.

10. Fraunfelder, FT. Hormones and agents affecting hormonal mechanisms. In: Fraunfelder, FT., editor. Drug-induced ocular side effects and drug interactions. Williams & Wilkins; 1996. p. 288-290.
11. Tripathi RC, Parapuram SK, Tripathi BJ, et al. Corticosteroids and glaucoma risk. *Drugs Aging* 1999;15:439–450. [PubMed: 10641955]
12. Black RL, Oglesby RB, von Sallman L, et al. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. *JAMA* 1960;174:166–171. [PubMed: 13801171]
13. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med* 1995;98:196–208. [PubMed: 7847437]
14. Dluhy RG. Effect of inhaled beclomethasone dipropionate and budesonide on adrenal function, skin changes and cataract formation. *Respir Med* 1998;92:15–23. [PubMed: 10193531]
15. Urban RC Jr, Cotlier E. Corticosteroid-induced cataracts. *Surv Ophthalmol* 1986;31:102–110. [PubMed: 3541262]
16. Maiorca R, Cristinelli L, Brunori G, et al. Prospective controlled trial of steroid withdrawal after six months in renal transplant patients treated with cyclosporine. *Transplant Proc* 1988;20:121–125. [PubMed: 3291224]
17. Tarantino A, Aroldi A, Stucchi L, et al. A randomized prospective trial comparing cyclosporine monotherapy with triple drug therapy in renal transplantation. *Transplantation* 1991;52:53–57. [PubMed: 1858154]
18. Ponticelli S, Pisani F, Montagnino G, et al. A randomized study comparing cyclosporine alone versus double and triple therapy in renal transplants. *Transplant Proc* 1997;29:290–291. [PubMed: 9123000]
19. Shun-Shin GA, Brown NP, Bron AJ, et al. Dynamic nature of posterior subcapsular cataracts. *Br J Ophthalmol* 1989;73:522–527. [PubMed: 2757992]
20. Chylack LT. Cataracts and inhaled corticosteroids. *N Engl J Med* 1997;337:46–48. [PubMed: 9203433]
21. Karim AK, Jacob TJ, Thompson GM. The human lens epithelium; morphologic and ultrastructural changes associated with steroid therapy. *Exp Eye Res* 1989;48:215–224. [PubMed: 2924809]
22. Harding, JJ.; Crabbe, MJC. The lens: development, proteins, metabolism and cataract. In: Orlando, DH., editor. *The eye*. 3. Vol. 1B. Academic Press; 1984. p. 207-492.
23. McLean JM. Use of ACTH and cortisone. *Tr Am Ophthalmol Soc* 1950;48:293–296.
24. Tripathi RC, Parapuram SK, Tripathi BJ, et al. Corticosteroids and glaucoma risk. *Drugs Aging* 1999;15:439–450. [PubMed: 10641955]
25. Skuta, GL.; Morgan, RK. Corticosteroid-induced glaucoma. In: Ritch, R.; Shields, MB.; Krupin, T., editors. *The glaucomas*. 2. Mosby; 1996. p. 1177-1188.
26. Garbe E, LeLoner J, Boivin JF, et al. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open angle glaucoma. *JAMA* 1997;277:722–727. [PubMed: 9042844]
27. Akduman L, Kolker AE, Black DL, et al. Treatment of persistent glaucoma secondary to periocular corticosteroids. *Am J Ophthalmol* 1996;122:275–277. [PubMed: 8694104]
28. Zhang X, Ognibene CM, Clark AF, et al. Dexamethasone inhibition of trabecular meshwork cell phagocytosis and its modulation by glucocorticoid receptor beta. *Exp Eye Res* 2007;84:275–284. [PubMed: 17126833]
29. Stone EM, Fingert JH, Alward WLM, et al. Identification of a gene that causes primary open angle glaucoma. *Science* 1997;275:668–670. [PubMed: 9005853]
30. Wiggs JL, Allingham RR, Vollrath D, et al. Prevalence of mutations in TIGR/myocilin in patients with adult and juvenile primary open-angle glaucoma. *Am J Hum Genet* 1998;63:1549–1552. [PubMed: 9792882]
31. Kubota R, Kudoh J, Mashima Y, et al. Genomic organization of the human myocilin gene (MYOC) responsible for primary open angle glaucoma (GLC1A). *Biochem Biophys Res Commun* 1998;242:396–400. [PubMed: 9446806]

32. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. *Invest Ophthalmol* 1965;4:187–197. [PubMed: 14283012]
33. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics: The effect of dexamethasone in the normal eye. *Arch Ophthalmol* 1963;70:482–491. [PubMed: 14078870]
34. Becker B, Hahn KA. Topical corticosteroids and heredity in primary open angle glaucoma. *Am J Ophthalmol* 1964;57:543–551. [PubMed: 14139296]
35. Paterson G. Studies of the response to topical dexamethasone of glaucoma relatives. *Trans Ophthalmol Soc UK* 1965;85:295–305. [PubMed: 5227191]
36. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. *Am J Ophthalmol* 1966;62:1039–1043.
37. Becker B. Diabetes mellitus and primary open angle glaucoma: the XXVII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1971;71:1–16. [PubMed: 5099936]
38. Gaston H, Absolon MJ, Thurtle OA, et al. Steroid responsiveness in connective tissue diseases. *Br J Ophthalmol* 1983;67:487–490. [PubMed: 6860617]
39. Black RL, Oglesby RB, Von Sallmann L, Bunim JJ. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. *JAMA* 1960;174:166–171. [PubMed: 13801171]
40. Palimeris G, Koliopoulos J, Velissaropoulos P. Ocular side effects of indomethacin. *Ophthalmologica* 1972;164:339–353. [PubMed: 4537509]
41. Palimeris G, Koliopoulos J, Velissaropoulos P. Electrophysiological findings in patients treated with indomethacin. *Adv Exp Med Biol* 1972;24:323–329. [PubMed: 4546798]
42. Graham CM, Blach RK. Indomethacin retinopathy: case report and review. *Br J Ophthalmol* 1988;72:434–438. [PubMed: 3291939]
43. Groomer AE, Terry JE, Westblom TU. Subconjunctival and external hemorrhage secondary to oral anticoagulation. *J Am Optom Assoc* 1990;61:770–775. [PubMed: 2246471]
44. Mortada A, Abboud I. Retinal haemorrhages after prolonged use of salicylates. *Br J Ophthalmol* 1973;57:199–200. [PubMed: 4707181]
45. Sharma VK, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS–TEN overlap: a retrospective study of causative drugs and clinical outcome. *Indian J Dermatol Venereol Leprol* 2008;74:238–240. [PubMed: 18583791]
46. Fraunfelder FW, Solomon J, Mehelas TJ. Ocular adverse effects associated with cyclooxygenase-2 inhibitors. *Arch Ophthalmol* 2006;124:277–279. [PubMed: 16476901]
47. Symmons DP, Salmon M, Farr M, et al. Sulfasalazine treatment and lymphocyte function in patients with rheumatoid arthritis. *J Rheumatol* 1988;15:575–579. [PubMed: 2899645]
48. Magnus JH, Elverland HH, Olsen EG, Husby G. Facial palsy and partial accommodative insufficiency associated with sulphasalazine treatment in a patient with ankylosing spondylitis. *Scand J Rheumatol* 1993;22:199–201. [PubMed: 8102809]
49. Santodomingo-Rubido J, Gilmartin B, Wolffsohn JS. Drug-induced bilateral transient myopia with the sulphonamide sulphasalazine. *Ophthalmic Physiol Opt* 2003;23:567–570. [PubMed: 14622362]
50. Fuentes-Páez G, Mendez MC, Montañez J, et al. Conjunctival pigmentation in Stevens–Johnson syndrome. *Ann Ophthalmol* 2007;39:152–157.
51. Abrams JR, Lebwohl MG, Guzzo CA, et al. CTLA4Ig-mediated blockade of T-cell co stimulation in patients with psoriasis vulgaris. *J Clin Invest* 1999;103:1243–1252. [PubMed: 10225967]
52. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907–1915. [PubMed: 14614165]
53. Aran AA, Putterman C. Treatment of lupus nephritis: facing the era of immunotherapy. *Panminerva Med* 2008;50:235–245. [PubMed: 18927528]
54. Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an

- inadequate response to anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008;67:547–554. [PubMed: 17921185]
55. Schiff M, Keiserman M, Coddling C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomized, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67:1096–1103. [PubMed: 18055472]
 56. Kremer JM, Genant HK, Moreland LW, et al. Results of a two-year follow-up study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum* 2008;58:953–963. [PubMed: 18383390]
 57. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;372:383–391. [PubMed: 18632147]
 58. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 2006;6:859–666. [PubMed: 16611321]
 59. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005;31:456–473. [PubMed: 16054760]
 60. Foran JM, Rohatiner AZ, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. *J Clin Oncol* 2000;18:317–324. [PubMed: 10637245]
 61. Lassoued S, Zabraniecki L, Marin F, Billey T. Toxoplasmic chorioretinitis and antitumor necrosis factor treatment in rheumatoid arthritis. *Semin Arthritis Rheum* 2007;36:262–263. [PubMed: 17067660]
 62. Fonollosa A, Segura A, Giralt J, Garcia-Arumi J. Tuberculous uveitis after treatment with etanercept. *Graefes Arch Clin Exp Ophthalmol* 2007;245:1397–1399. [PubMed: 17364199]
 63. Taban M, Dupps WJ, Mandell B, Perez VL. Etanercept (enbrel)-associated inflammatory eye disease: case report and review of the literature. *Ocul Immunol Inflamm* 2006;14:145–150. [PubMed: 16766397]
 64. Purvin VA. Anterior ischemic optic neuropathy secondary to interferon alfa. *Arch Ophthalmol* 1995;113:1041–1044. [PubMed: 7639655]
 65. Hayasaka S, Fujii M, Yamamoto Y, et al. Retinopathy and sub-conjunctival haemorrhage in patients with chronic viral hepatitis receiving interferon alfa. *Br J Ophthalmol* 1995;79:150–152. [PubMed: 7696235]
 66. O'Neill DP. The eye and liver disorders. *Eye* 1992;6:366–370. [PubMed: 1478307]
 67. Baratz KH, Fulcher SF, Bourne WM. Hepatitis C-associated keratitis. *Arch Ophthalmol* 1998;116:529–530. [PubMed: 9565055]
 68. Fukumoto Y, Shigemitsu T, Kajii N, et al. Abducent nerve paralysis during interferon alpha-2a therapy in a case of chronic active hepatitis C. *Intern Med* 1994;33:637–640. [PubMed: 7827383]
 69. Gillies MC, Garrett SK, Shina SM, Morlet N, Taylor HR. Topical interferon alpha 2b for corneal haze after excimer laser photorefractive keratectomy. *J Cataract Refract Surg* 1996;22:891–900. [PubMed: 9041079]
 70. Leyland M, Torok ME, Acheson J, Foster GR. Hepatitis C virus infection is not associated with a marked increase in the prevalence of ophthalmic morbidity. *Eye* 2000;14:889–891. [PubMed: 11584849]
 71. Tokai R, Ikeda T, Miyaura T, Sato K. Interferon-associated retinopathy and cystoid macular edema. *Arch Ophthalmol* 2001;119:1077–1079. [PubMed: 11448335]
 72. Peres-Alvarez AF, Jimenez-Alonso J, Reche-Molina I, et al. Retinal vasculitis and vitreitis in a patient with chronic hepatitis C virus. *Arch Intern Med* 2001;161:2262. [PubMed: 11575987]
 73. Jain K, Lam WC, Waheeb S, Thai Q, Heathcote J. Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001;85:1171–1173. [PubMed: 11567959]
 74. Esmaeli B, Koller C, Papadopoulos N, Romaguera J. Interferon-induced retinopathy in asymptomatic cancer patients. *Ophthalmology* 2001;108:858–860. [PubMed: 11320013]

75. Willson RL, Ross RD, Willson LM, et al. Interferon-associated retinopathy in a young, insulin dependent diabetic patient. *Retina* 2000;20:413–415. [PubMed: 10950429]
76. Norcia F, Di Maria A, Prandini F, Redaelli C. Natural interferon therapy: optic nerve ischemic damage? *Ophthalmologica* 1999;213:339–340. [PubMed: 10516525]
77. Kadayifcilar S, Boyacioglu S, Kart H, Gursoy M, Aydin P. Ocular complications with high-dose interferon alpha in chronic active hepatitis. *Eye* 1999;13:241–246. [PubMed: 10450390]
78. Abe T, Nakajima A, Matsunaga M, Sakuragi S, Komatsu M. Decreased tear lactoferrin concentration in patients with chronic hepatitis C. *Br J Ophthalmol* 1999;83:684–687. [PubMed: 10340976]
79. Manesis EK, Moschos M, Brouzas D, et al. Neurovisual impairment: a frequent complication of alpha-interferon treatment in chronic viral hepatitis. *Hepatology* 1998;27:1421–1427. [PubMed: 9581701]
80. Sugano S, Suzuki T, Watanabe M, et al. Retinal complications and plasma C5a levels during interferon alpha therapy for chronic hepatitis C. *Am J Gastroenterol* 1998;93:2441–2444. [PubMed: 9860406]
81. Kawano T, Shigehira M, Uto H, et al. Retinal complications during interferon therapy for chronic hepatitis C. *Am J Gastroenterol* 1996;91:309–313. [PubMed: 8607498]
82. Guyer DR, Tiedeman J, Yannuzzi LA, et al. Interferon-associated retinopathy. *Arch Ophthalmol* 1993;111:350–356. [PubMed: 8447745]
83. Schulman JA, Liang C, Kooragayala LM, King J. Posterior segment complications in patients with hepatitis C treated with interferon and ribavirin. *Ophthalmology* 2003;110:437–442. [PubMed: 12578794]
84. Hejny C, Sternberg P, Lawson DH, Greiner K, Aaberg TM Jr. Retinopathy associated with high-dose interferon alfa-2b therapy. *Am J Ophthalmol* 2001;131:782–787. [PubMed: 11384576]
85. Yamada H, Mizobuchi K, Isogai Y. Acute onset of ocular complications with interferon. *Lancet* 1994;343:914. [PubMed: 7908371]
86. Kuga K, Hasumura S, Nagamori S, Toda G, Kitahara K. Intraocular hemorrhage developing during interferon therapy. *Intern Med* 1996;35:15–18. [PubMed: 8652925]
87. Al-Tweigeri T, Nabholz JM, Mackey JR. Ocular toxicity and cancer chemotherapy. *Cancer* 1996;78:1359–1373. [PubMed: 8839540]
88. Margileth DA, Poplack DG, Pizzo PA, et al. Blindness during remission in two patients with acute lymphoblastic leukemia: a possible complication of multimodality therapy. *Cancer* 1997;39:58–61. [PubMed: 264409]
89. Clare G, Colley S, Kennett R, et al. Reversible optic neuropathy associated with low-dose methotrexate therapy. *J Neuroophthalmol* 2005;25:109–112. [PubMed: 15937433]
90. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology* 2004;43:267–271. [PubMed: 14963199]
91. Ponjavic V, Granse L, Stigmar EB, et al. Reduced full-field electroretinogram (ERG) in a patient treated with methotrexate. *Acta Ophthalmol Scand* 2004;82:96–99. [PubMed: 14982050]
92. Razonable RR, Pulido JS, Deziel PJ, et al. Chorioretinitis and vitreitis due to *Tropheryma whipplei* after transplantation: case report and review. *Transpl Infect Dis* 2008;10:413–418. [PubMed: 18564981]
93. Hassikou H, El Haouri M, Tabache M, et al. Leflunomide-induced toxic epidermal necrolysis in a patient with rheumatoid arthritis. *Joint Bone Spine* 2008;75:597–599. [PubMed: 18805724]
94. de Nijs RN, Jacobs JW, Lems WF, et al. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. *N Engl J Med* 2006;355:675–684. [PubMed: 16914703]
95. Valleala H, Laitinen K, Pyllkanen L, et al. Clinical and biochemical response to single infusion of clodronate in active rheumatoid arthritis – a double blind placebo controlled study. *Inflamm Res* 2001;50:598–601. [PubMed: 11822785]
96. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. *N Engl J Med* 2003;348:1187–1188. [PubMed: 12646685]
97. Fraunfelder FW. Ocular side effects associated with bisphosphonates. *Drugs Today* 2003;39:829–835. [PubMed: 14702129]

98. Fraunfelder FW, Fraunfelder FF, Jensvold B. Scleritis and other ocular side effects associated with pamidronate disodium. *Am J Ophthalmol* 2003;135:219–222. [PubMed: 12566027]
99. Payne JF. A postgraduate lecture on lupus erythematosus. *Clin J* 1894;4:223–229.
100. Schadewaldt H. Introduction of atebine into material medica. *Dtsch Med Wochenschrift* 1975;100:2583–2585.
101. Green R. A report of fifty cases of malaria treated with atebine. *Lancet* 1932;1:826–829.
102. Schulemann W. Synthetic antimalarial drugs. *Br Med J* 1932;1:100–101.
103. Carr RE, Henkind P, Rothfield N, et al. Ocular toxicity of anti-malarial drugs: long term follow-up. *Am J Ophthalmol* 1968;66:738–744. [PubMed: 5729592]
104. Ansdell VE, Common JD. Corneal changes induced by mepacrine. *J Trop Med Hyg* 1979;82:206–207. [PubMed: 529354]
105. Chamberlain WP Jr, Boles DJ. Edema of cornea precipitated by quinacrine (Atabrine). *Arch Ophthalmol* 1946;35:120–134.
106. Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. *Lancet* 1959;2:478–480. [PubMed: 14402143]
107. Shearer RV, Dubois EL. Ocular changes induced by long term hydroxychloroquine (Plaquenil) therapy. *Am J Ophthalmol* 1967;64:245–252. [PubMed: 6036279]
108. Levy GD, Munz SJ, Paschal J, et al. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum* 1997;40:1482–1486. [PubMed: 9259429]
109. Klinger G, Morad Y, Westall CA, et al. Ocular toxicity and ante-natal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. *Lancet* 2001;358:813–814. [PubMed: 11564493]
110. Yam J, Kwok A. Ocular toxicity of hydroxychloroquine. *Hong Kong Med J* 2006;12:294–304. [PubMed: 16912357]
111. Jones SK. Ocular toxicity and hydroxychloroquine: Guidelines for screening. *Br J Dermatol* 1999;140:37.
112. Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF. Recommendations on screening for chloroquine and hydroxy-chloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology* 2002;109:1377–1382. [PubMed: 12093666]
113. Marmor MF. New American Academy of Ophthalmology recommendations on screening for hydroxychloroquine retinopathy. *Arthritis Rheum* 2003;48:1764. [PubMed: 12794848]
114. Easterbrook M. Screening for antimalarial toxicity: current concepts. *Can J Ophthalmol* 2002;37:325–328. [PubMed: 12422914]
115. Royal College of Ophthalmologists.
http://www.rcophth.ac.uk/docs/publications/published-guidelines/Hydroxychloroquine_and_Ocular_Toxicity_final_Oct_2009.pdf
116. American College of Rheumatology. Position Statement: Screening for Hydroxychloroquine Retinopathy. <http://www.rheumatology.org/publications/position/hydroxy.asp?aud=prs>
117. Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. *Ann Rheum Dis* 1997;56:188–190. [PubMed: 9135223]
118. Johnson MW, Vine AK. Hydroxychloroquine therapy in massive total doses without retinal toxicity. *Am J Ophthalmol* 1987;104:139–144. [PubMed: 3618711]
119. Shroyer NF, Lewis RA, Lupski JR. Analysis of the ABCR (*ABCA4*) gene in 4-aminoquinoline retinopathy. *Am J Ophthalmol* 2001;131:761–766. [PubMed: 11384574]
120. Wei LC, Chen SN, Ho CL, Kuo YH, Ho JD. Progression of hydroxychloroquine retinopathy after discontinuation of therapy: Case report. *Chang Gung Med J* 2001;24:329–334. [PubMed: 11480331]

Table 1

Common antirheumatic drugs causing important ocular adverse drug reactions

Drug classification and generic (brand name)	Potential visual or sight-threatening complications	Clinical management recommendations
Chloroquine (Aralen)/hydroxychloroquine (Plaquenil)	Blurred vision, headache, accommodative dysfunction, vortex keratopathy, irreversible retinal damage in patients on long-term high dose therapy (e.g. bull's eye maculopathy)	Need for screening every 6 months with visual acuity, central threshold visual field, Amsler grid, color vision testing and funduscopy. Repeat fundus photography periodically, as indicated. Electroretinogram (ERG) testing is optional; may consider if clinical findings are progressive, equivocal or unreliable
Prednisone	Posterior subcapsular cataract, increased intraocular pressure, open angle glaucoma	Need for screening with slit-lamp examinations conducted three or four times a year for patients on long-term therapy and twice a year for patients taking intermittent topical ocular or systemic steroids