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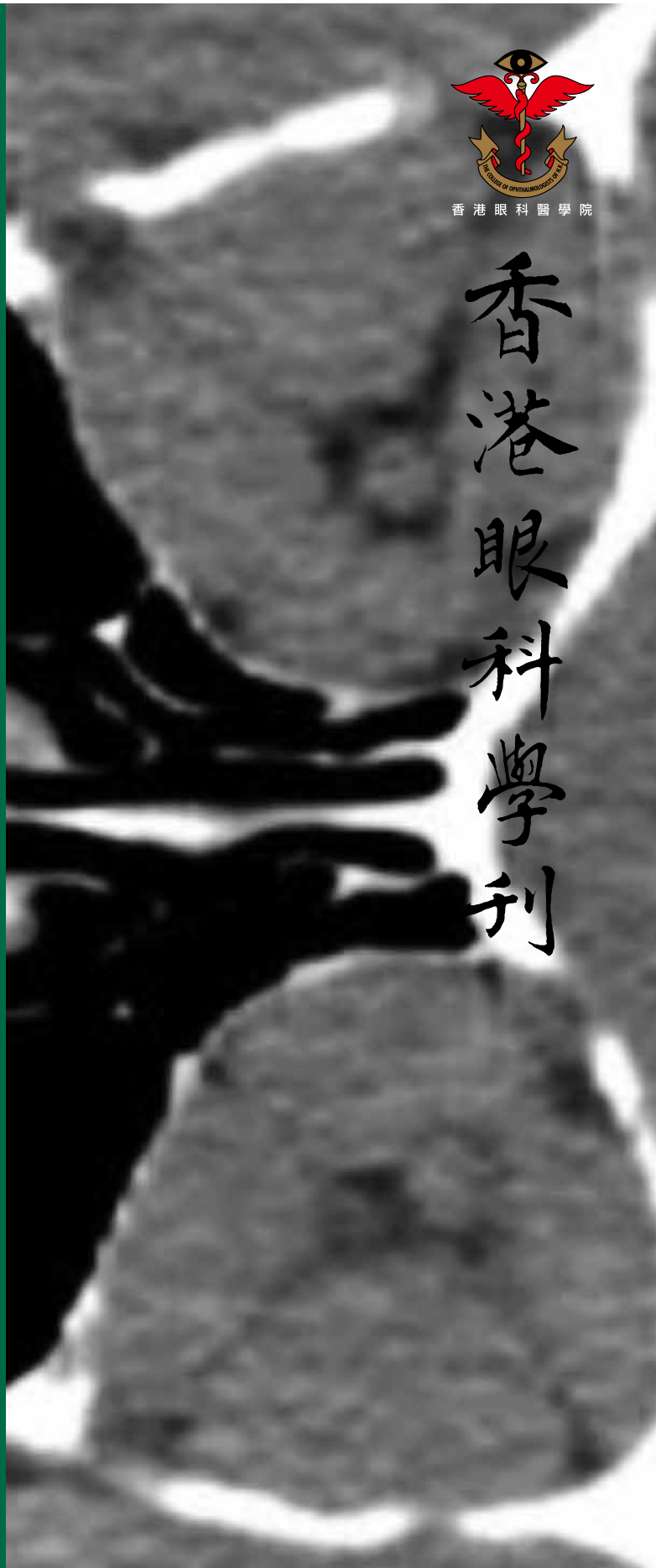

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1. *International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. ICMJE; April 2010. www.icmje.org*

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EDITORIAL

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Thyroid eye disease: endocrinologist, endocrine surgeon, and ophthalmologist perspectives

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Thyroid eye disease presents with a range of orbital and ocular manifestations associated with thyroid dysfunction, usually secondary to an autoimmune condition or Graves disease. Other conditions such as Hashimoto's thyroiditis, thyroid carcinoma, primary hyperthyroidism, and primary hypothyroidism can also result in thyroid eye disease. Orbital involvement is the most common extrathyroidal manifestation. Graves disease affects up to 2% of the female and 0.2% of the male population.[1] Up to 20 to 25% of patients with Graves disease will have eye involvement at the initial diagnosis and up to 50% of patients will develop it during the course of disease.[2] Up to 3 to 5% of patients have severe involvement.[3]

The pathogenesis of ophthalmopathy secondary to thyroid disease is not entirely understood. An autoimmune inflammatory process that targets orbital and periorbital tissue can result in debilitating diplopia, proptosis, eyelid retraction, exposure keratopathy, glaucoma, and irreversible optic neuropathy.[4,5] Even in mild cases, quality of life can be affected.[6] The condition can be disfiguring and have a major psychosocial impact on patients and their family. Complications such as dysthyroid optic neuropathy, glaucoma, exposure keratopathy, and globe subluxation may result in irreversible vision loss. To further complicate matters, thyroid eye disease can manifest differently in Asian populations and its management may differ to that reported in the western literature.[7] The European Group on Graves' orbitopathy has published a consensus statement on management of the disease.[5] Its latest guidelines emphasize the need for patient-centered management to improve quality of life and psychosocial well-being, as is the need to promptly restore and maintain stable euthyroidism.[8] The course of thyroid eye disease can progress rapidly in patients who smoke, have fluctuating thyroid function, or are prescribed radioactive iodine for hyperthyroidism.[5] In a nationwide survey in the UK, only 56% of responders were satisfied with the management of their thyroid eye disease.[9] Multidisciplinary collaboration between different specialties to provide a patient-centered and holistic approach is vital.

In this issue, we have invited experts in different aspects of thyroid and thyroid eye disease to provide updated perspectives for management. We have included the perspectives of an endocrinologist, an endocrine surgeon, and an ophthalmologist to provide an all-encompassing understanding of this systemic-ophthalmic condition. From an endocrinologist perspective, Lee[10] stress the importance of anti-thyroid medication such as thionamides to attain optimal control of thyroid function. Patients may need to

be referred for thyroidectomy when euthyroidism is not achieved by medication alone or a more definitive treatment is desired. From an endocrine surgeon perspective, Man and Lang[11] highlight the advantage of surgical thyroidectomy for rapid resolution of thyroid dysfunction without the risks associated with radioactive iodine. From an ophthalmologist perspective, Chong and Lai[7] report their experience from the first thyroid eye clinic in Hong Kong. A multidisciplinary approach enables more efficient patient-care. Surgical intervention may be necessary for vision-threatening complications not amendable by immunosuppressants.[7] In stable disease, rehabilitative surgery may be appropriate to correct residual abnormalities such as proptosis, strabismus, and eyelid malposition to improve function and esthetic outcome. The skills of an oculoplastic and strabismus surgeon are often required.

Thyroid eye disease exemplifies the importance of a collaborative multidisciplinary approach for patient-centered care to achieve optimal outcome and patient satisfaction.

As this is the final issue of the *Hong Kong Journal of Ophthalmology* (HKJO) published by the current Editorial Board, the Editor would like to take this special occasion to thank all contributors, scientific reviewers, and members of the Editorial Board for their invaluable input during the past two years. During which, HKJO has made a big leap forward from being a print journal to a print-and-electronic journal indexed on Google Scholar. We have built a dedicated website with online submission capability. The Editorial Board would like to thank Dr Alvin Au for his tremendous work in setting up and maintaining the website. This would not have been made possible without the generous support from the College, and of utmost importance, from our readers.

References

1. *Hegedus L. Treatment of Graves' hyperthyroidism: evidence-based and emerging modalities. Endocrinol Metab Clin North Am. 2009;38:355-71.*
2. *Goh SY, Ho SC, Seah LL, Fong KS, Khoo DH. Thyroid autoantibody profiles in ophthalmic dominant and thyroid dominant Graves' disease differ and suggest ophthalmopathy is a multiantigenic disease. Clin Endocrinol (Oxf). 2004;60:600-7.*
3. *Werner SC. Classification of the eye changes of Grave's disease. J Clin Endocrinol Metab. 1969;29:982-4.*
4. *Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf). 1977;7:481-93.*
5. *Bartalena L, Baldeschi L, Dickinson A, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008;158:273-85.*
6. *Marcocci C, Kahaly GJ, Krassas GE, et al. Selenium and the course of mild Graves' orbitopathy. N Engl J Med. 2011;364:1920-31.*
7. *Chong KK, Lai TH. Thyroid eye disease: a 2017 update from the first thyroid eye clinic in Hong Kong. Hong Kong J Ophthalmol. 2017;21:11-8.*
8. *Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5:9-26.*
9. *Estcourt S, Hickey J, Perros P, Dayan C, Vaidya B. The patient experience of services for thyroid eye disease in the United Kingdom: results of a nationwide survey. Eur J Endocrinol. 2009;161:483-7.*
10. *Lee CH. Medical therapy for thyrotoxicosis. Hong Kong J Ophthalmol. 2017;21:7-8.*
11. *Man V, Lang BH. Surgical treatment for Graves' disease. Hong Kong J Ophthalmol. 2017;21:9-10.*

Review Article

Medical therapy for thyrotoxicosis

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Abstract

Thyrotoxicosis is a prevalent endocrine disorder. This study reviews the effects and side effects of thionamides in medical therapy for thyrotoxicosis.

Thyrotoxicosis is a prevalent endocrine disorder. Common etiologies include Graves' disease and toxic multinodular goiter.[1] Anti-thyroid drugs (ATD) are the primary treatment modality especially in Graves' disease, or the bridging therapy to stabilize thyroid function prior to definitive treatment with either radioactive iodine or surgery.[2] With regard to Graves' ophthalmopathy, in contrast to radioactive iodine treatment that confers a definite yet small risk of development or exacerbation of thyroid eye disease, ATD is at least neutral, or may improve, the natural course of the disease by correction of thyrotoxicosis.[3] Thionamides, which include methimazole (MMI) and its precursor carbimazole (CMZ), as well as the derivatives of thiouracil, prophylthiouracil (PTU), are commonly prescribed ATDs.

Thionamides inhibit the thyroid peroxidase-catalyzed iodination of tyrosine residues, thereby decreasing thyroid hormone synthesis. In Graves' disease, thionamides also have an effect on the reduction of intrathyroidal immune dysregulation. Serum concentrations of anti-thyrotropin-receptor antibodies decrease over time in patients prescribed thionamides.[4] In addition, PTU blocks the peripheral conversion of thyroxine to tri-iodothyronine, and is preferred in the setting of thyroid storm.[2,4] Under most clinical circumstances, current guidelines recommend MMI/CMZ over PTU in patients who choose medical therapy for Graves' disease.[2]

Most side effects of MMI/CMZ are dose-related, unlike those of PTU. Minor side effects of thionamides include cutaneous reactions, usually in the form of urticaria or macular eruption (4-6%), gastrointestinal upset and arthralgias (1-5%). Although cross-reactivity exists between MMI/CMZ and PTU, in the case of minor cutaneous reactions, use of an antihistamine and/or switching from one ATD to another should suffice. Discontinuation of ATD might be necessary for arthralgias and other major side effects.[4] Arthralgias may precede a severe form of transient migratory polyarthritis.[4]

Agranulocytosis, defined as an absolute granulocyte count $<0.5x10^9$/L, is a rare but life-threatening adverse effect of ATDs. Its estimated frequency is about 0.1-0.5% and it occurs equally among patients receiving MMI/CMZ (0.37%) or PTU (0.35%).[4] Although mild, transient granulocytopenia might be present in Graves' disease, ATDs are contraindicated if the pre-treatment absolute neutrophil count is $<0.5x10^9$/L.[2] Agranulocytosis mostly occurs acutely within the first 3 months of treatment. Unless patients develop fever or pharyngitis, routine monitoring of white blood cell count is not recommended.[2] Nonetheless, a prior uneventful course of ATDs does not preclude the development of agranulocytosis in subsequent treatment courses.[4]

In a genome-wide association study comparing 20 Chinese patients with ATD-induced agranulocytosis with 775 healthy controls, *HLA-B*38:02:01* was identified as the susceptibility locus of MMI/CMZ-related agranulocytosis, with an odds ratio of 265.5 (95% confidence interval = 27.9-2528.0, $p = 2.5x10^{-14}$), a positive predictive value of 0.07, a negative predictive value of 0.999, and the number needed to screen to prevent a single case of MMI/CMZ-related agranulocytosis of 211.[5] *HLA-B*38:02:01* is common in some Southeast Asian countries and may be a useful pharmacogenetic marker to predict MMI/CMZ-related agranulocytosis.[5] Although agranulocytosis is thought to be autoimmune mediated, *HLA-B*38:02:01* is not associated with PTU-related agranulocytosis, highlighting the possible differences in genetic risk-markers, as well as mechanisms that underlie the development of agranulocytosis for each ATD.[5]

Hepatotoxicity is another major adverse effect of ATDs estimated to occur in 0.1-0.2% of patients taking thionamides.[4] Thionamides are contraindicated if liver transaminase level is more than fivefold above the upper limit of the normal reference range prior to drug initiation.[2] This takes into account the fact that mild hepatic dysfunction

related to thyrotoxicosis itself is not uncommon. Typically, MMI/CMZ-related hepatotoxicity is cholestatic. In a study of serial changes in liver function before and during MMI treatment in 77 newly diagnosed thyrotoxic patients, mild elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels was noted at baseline in approximately one third of patients.[6] Most had ALT/AST levels around twice the upper limit of normal. In such patients, MMI treatment resulted in a rapid increase in ALT/AST level. In those with normal liver function, MMI treatment also induced mild ALT/AST elevation, usually around twice the upper limit of normal.[6] In contrast to MMI/CMZ, PTU may cause immunoallergic hepatitis that can deteriorate to fulminant hepatic failure.[2,4] Although asymptomatic elevation of serum ALT/AST level up to six times the upper limit of normal with spontaneous resolution has been reported, current guidelines recommend discontinuation of PTU if serum transminase level is elevated to more than two to threefold the upper limit of normal and fail to improve within one week.[2] After normalization of serum transminase level, MMI/CMZ can be cautiously initiated with regular monitoring of liver function.

Some adverse effects are shared among all thionamides, although some are more common in one ATD than others or exclusive to MMI/CMZ or PTU. Antineutrophil cytoplasmic antibody positive vasculitis is more commonly associated with PTU than MMI/CMZ.[2,4] One hypothesis relates to the formation of reactive intermediates from the oxidation of PTU by myeloperoxidase, which might explain the preponderance of this adverse effect in PTU.[7] In addition, although antineutrophil cytoplasmic antibody positivity occurs more frequently with prolonged exposure to PTU beyond 18 months, the overall risk of developing small vessel vasculitis remains low.[7] Small vessel inflammation can affect all organs, particularly the kidneys, lungs, and skin. The prognosis after ATD discontinuation is generally good.[7] MMI/CMZ-specific adverse events include teratogenic effects such as aplasia cutis, choanal or esophageal atresia. Thus, use of PTU is recommended during the first trimester of pregnancy.[2]

Current guidelines recommend ATD treatment of 12-18 months for Graves' disease, as prolonged treatment beyond 18 months is not associated with an improved remission rate.[8] Predictors of relapse in patients with newly diagnosed Graves' disease before the initiation of ATD treatment include young age (<40 years), higher free thyroxine level (≥40 pmol/L), higher serum thyrotropin-binding inhibitor immunoglobulin (>6 IU/L), larger goiter at diagnosis, *HLA* subtypes *DQ1B*02*, *DQA1*05*, and *DRB1*03*, and PTPN22 C/T polymorphism.[9] In general, 50% of patients relapse after the initial remission.[1] Definitive treatment with either radioactive iodine or total thyroidectomy is recommended for relapsed disease. Nonetheless, a prolonged course of low-dose MMI treatment (median follow-up of 71.3±40.3 months) achieves a better clinical activity score than radioactive iodine does and is a safe and effective alternative, in particular for those with mild Graves' ophthalmopathy.[10]

There are many other medications for thyrotoxicosis. Beta-blockers should be considered in all patients with symptomatic thyrotoxicosis, unless contraindicated.[2] Lugol's iodine and potassium iodide are also important, especially preoperatively or in the setting of thyroid storm.[2] Lithium, usually given at a dose of 250mg thrice daily, is a useful alternative when thionamides are intolerable or contraindicated.[11] Lithium is an effective adjunct to radioactive iodine as it increases radioiodine retention and keeps the radiation dose to a minimum.[12,13]

To conclude, although monoclonal anti-thyrotropin-receptor antibodies are potential therapeutics for thyrotoxicosis,[14] thionamides and PTU remain inexpensive, tolerable, and simple-to-use ATDs.

References

1. *Burch HB, Cooper DS. Management of Graves disease: a review. JAMA. 2015;314:2544-54.*
2. *Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract. 2011;17:456-520.*
3. *Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5:9-26.*
4. *Cooper DS. Antithyroid drugs. N Engl J Med. 2005;352:905-17.*
5. *Cheung CL, Sing CW, Tang C, et al. HLA-B*38:02:01 predicts carbimazole/methimazole-induced agranulocytosis. Clin Pharmacol Ther. 2016;99:555-61.*
6. *Niculescu DA, Dusceac R, Galoiu SA, Capatina CA, Poiana C. Serial changes of liver function tests before and during methimazole treatment in thyrotoxic patients. Endocr Pract. 2016;22:974-9.*
7. *Balavoine AS, Glinoer D, Dubucquoi S, Wemeau JL. Antineutrophil cytoplasmic antibody-positive small-vessel vasculitis associated with antithyroid drug therapy: how significant is the clinical problem? Thyroid. 2015;25:1273-81.*
8. *Abraham P, Avenell A, Park CM, Watson WA, Bevan JS. A systematic review of drug therapy for Graves' hyperthyroidism. Eur J Endocrinol. 2005;153:489-98.*
9. *Vos XG, Endert E, Zwinderman AH, Tijssen JG, Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab. 2016;101:1381-9.*
10. *Villagelin D, Romaldini JH, Santos RB, Milkos AB, Ward LS. Outcomes in relapsed Graves' disease patients following radioiodine or prolonged low dose of methimazole treatment. Thyroid. 2015;25:1282-90.*
11. *Ng YW, Tiu SC, Choi KL, et al. Use of lithium in the treatment of thyrotoxicosis. Hong Kong Med J. 2006;12:254-9.*
12. *Bogazzi F, Bartalena L, Brogioni S, et al. Comparison of radioiodine with radioiodine plus lithium in the treatment of Graves' hyperthyroidism. J Clin Endocrinol Metab. 1999;84:499-503.*
13. *Turner JG, Brownlie BE, Rogers TG. Lithium as an adjunct to radioiodine therapy for thyrotoxicosis. Lancet. 1976;1:614-5.*
14. *Davies TF, Latif R. Targeting the thyroid-stimulating hormone receptor with small molecule ligands and antibodies. Expert Opin Ther Targets. 2015;19:835-47.*

Review Article

Surgical treatment for Graves' disease

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Background

Graves' disease (GD) is the most common cause of hyperthyroidism. It accounts for 60 to 80% of all cases of hyperthyroidism and has a female preponderance.[1] Approximately 3% of women and 0.5% of men are at risk of GD in their lifetime.[2] It is caused by the presence of auto-antibodies against the thyroid-stimulating hormone receptor (TSHR) leading to hyperplasia and hypertrophy of the thyroid follicles, resulting in manifestations of hyperthyroidism, ophthalmopathy, and dermopathy.[1] GD is mostly diagnosed clinically. In addition to elevated levels of free T4, triiodothyronine, and suppressed TSHR levels, patients tend to have a symmetrically enlarged goitre with or without ophthalmopathy. In patients with less typical manifestations, the presence of elevated TSHR auto-antibodies (TRAb) and diffuse radioactive iodine uptake may aid in the diagnosis.[1-3]

Anti-thyroid medications, radioactive iodine, and surgery are common treatment modalities for GD. Nonetheless, the optimal treatment remains controversial and the choice varies between different institutions and countries. A survey focusing on clinical practice patterns in different parts of the world reported that radioactive iodine was the preferred treatment in North America, with over half of patients taking it as first-line treatment, while anti-thyroid medication was the preferred first-line treatment in most parts of Europe and Asia.[4,5] In Hong Kong, GD patients are often initially managed with anti-thyroid medication for up to 18-20 months. When the disease relapses or the patient could no longer tolerate anti-thyroid medication, radioactive iodine or surgery is offered.[6]

In certain clinical circumstances, surgery is the preferred first-line treatment for GD. Examples include those hoping to become pregnant within 6 months and those suspected of having suspicious or malignant thyroid nodules or local compressive symptoms.[2,3,6,7] Incidental thyroid carcinoma in the thyroid specimen is not uncommon with an incidence of 4-10%.[8-10] Surgery enables a rapid resolution of hyperthyroidism, while anti-thyroid medications and radioactive iodine may take up to 6-12 weeks.[1]

Some patients with GD have extrathyroidal manifestations. Graves' ophthalmopathy is one of the most clinically apparent manifestations and affects approximately 25% of all patients with GD.[2] It may worsen diplopia and optic neuropathy.[1] Some consider its presence an indication for surgery because radioactive iodine tends to worsen its severity at least initially. Surgery enables a gradual decrease in serum TRAb, while radioiodine iodine tends to cause an initial surge of TRAb.[11] Randomized controlled trials and systemic reviews suggest a higher risk of new-onset or further worsening of pre-existing Graves' ophthalmopathy after radioactive iodine.[12-14] Therefore, prophylactic corticosteroid is often given before the administration of radioactive iodine.[14]

Surgery for Graves' disease

Subtotal thyroidectomy were widely advocated and practiced until the 1990s.[3] For subtotal thyroidectomy, a large thyroid remnant (up to 10g) is usually left on one or both sides of the thyroid bed with an aim to maintain euthyroidism without the need for thyroxine replacement. Nonetheless, euthyroidism is usually not achievable in the long term for most patients. In a meta-analysis of western populations, only 60% of patients who underwent subtotal thyroidectomy achieved euthyroidism after a mean follow-up of 5.6 years.[8] For Asians, 72% of patients who underwent subtotal thyroidectomy required thyroxine replacement eventually.[15,16] Therefore, total thyroidectomy is usually the preferred choice, because it is associated with almost no chance of disease relapse and is comparable with subtotal

thyroidectomy in terms of morbidities when peformed in experienced hands. One study even reported less blood loss in total thyroidectomy.[15] The rate of permanent recurrent laryngeal nerve palsy is comparable in total and subtotal thyroidectomy.[8-10,17,18] The major drawback of total thyroidectomy is the slightly higher risk of postoperative temporary and permanent hypoparathyroidism.[6,9] As a result, both the updated American Thyroid Association and the American Association of Clinical Endocrinologists recommend total or near-total thyroidectomy (<2g remnant) as the surgery of choice for GD.[19] In our hospital, since the adoption of total over subtotal thyroidectomy in 2000, the rate of complications has remained acceptably low.[6] In addition, total thyroidectomy decreases the rates of failure and recurrence and complications associated with re-operation. It is considered a cost-effective treatment when medical treatment fails.[20]

Conclusions

In Hong Kong, surgery or thyroidectomy is usually reserved for patients with a GD relapse following 18 months or longer prescription of anti-thyroid medications. It is recommended as first-line treatment when a rapid resolution of thyrotoxic symptoms is desired, in those with suspected thyroid malignancy, or in the presence of local compressive symptoms. Total thyroidectomy is preferred over partial or subtotal thyroidectomy.

References

1. *Weetman AP. Graves' disease. N Engl J Med. 2000;343:1236-48.*
2. *Burch HB, Cooper DS. Management of Graves disease: a review. JAMA. 2015;314:2544-54.*
3. *Schüssler-Fiorenza CM, Bruns CM, Chen H. The surgical management of Graves' disease. J Surg Res. 2006;133:207-14.*
4. *Burch HB, Burman KD, Cooper DS. A 2011 survey of clinical practice patterns in the management of Graves' disease. J Clin Endocrinol Metab. 2012;97:4549-58.*
5. *Bartalena L, Burch HB, Burman KD, Kahaly GJ. A 2013 European survey of clinical practice patterns in the management of Graves' disease. Clin Endocrinol (Oxf). 2016;84:115-20.*
6. *Yip J, Lang BH, Lo CY. Changing trend in surgical indication and management for Graves' disease. Am J Surg. 2012;203:162-7.*
7. *Alsanea O, Clark OH. Treatment of Graves' disease: the advantages of surgery. Endocrinol Metab Clin North Am. 2000;29:321-37.*
8. *Palit TK, Miller CC 3rd, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res. 2000;90:161-5.*
9. *Feroci F, Rettori M, Borrelli A, et al. A systematic review and meta-analysis of total thyroidectomy versus bilateral subtotal thyroidectomy for Graves' disease. Surgery. 2014;155:529-40.*
10. *Bojic T, Paunovic I, Diklic A, et al. Total thyroidectomy as a method of choice in the treatment of Graves' disease: analysis of 1432 patients. BMC Surg. 2015;15:39.*
11. *Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. Eur J Endocrinol. 2008;158:69-75.*
12. *Tallstedt L, Lundell G, Tørring O, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. N Engl J Med. 1992;326:1733-8.*
13. *Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 1998;338:73-8.*
14. *Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf). 2008;69:943-50.*
15. *Ku CF, Lo CY, Chan WF, Kung AW, Lam KS. Total thyroidectomy replaces subtotal thyroidectomy as the preferred surgical treatment for Graves' disease. ANZ J Surg. 2005;75:528-31.*
16. *Sung TY, Lee YM, Yoon JH, Chung KW, Hong SJ. Long-term effect of surgery in Graves' disease: 20 years experience in a single institution. Int J Endocrinol. 2015;2015:542641.*
17. *Stalberg P, Svensson A, Hessman O, Akerstrom G, Hellman P. Surgical treatment of Graves' disease: evidence-based approach. World J Surg. 2008;32:1269-77.*
18. *Al-Adhami A, Snaith AC, Craig WL, Krukowski ZH. Changing trends in surgery for Graves' disease: a cohort comparison of those having surgery intended to preserve thyroid function with those having ablative surgery. J Otolaryngol Head Neck Surg. 2013;42:37.*
19. *Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343-421.*
20. *In H, Pearce EN, Wong AK, Burgess JF, McAneny DB, Rosen JE. Treatment options for Graves disease: a cost-effectiveness analysis. J Am Coll Surg. 2009;209:170-9.*

Review Article

Thyroid eye disease: a 2017 update from the first thyroid eye clinic in Hong Kong

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Abstract

Thyroid eye disease (TED) is the most important extra-thyroidal manifestation of the most common autoimmune disease worldwide. In this review, we summarized its clinical features into 5D and its management into 8S. We also shared our past 6 years' experience of managing nearly 700 TED patients in the first thyroid eye clinic in Hong Kong.

Nomenclature of thyroid eye disease

Thyroid eye disease (TED) is also known as Graves' ophthalmopathy/orbitopathy, thyroid-associated ophthalmopathy/orbitopathy, or thyrotoxic/endocrine exophthalmos. It is the most important extrathyroidal manifestation of autoimmune thyroid diseases (AITD) including Graves' disease and Hashimoto thyroiditis. It is also the most common orbital disorder in adults worldwide and the most common cause of unilateral or bilateral axial proptosis (exophthalmos), acquired strabismus or lid retraction.[1] TED may lead to 5Ds: visual Dysfunction, Double vision, ocular Discomfort, facial Disfigurement, and significantly Decreased quality of life.[2]

Disease spectrum of thyroid eye disease

Patients with TED may not have any clinical or biochemical evidence of thyroid dysfunction or associated antibodies. They may have isolated orbital involvement known as ophthalmic Graves' disease or euthyroid Graves' ophthalmopathy, which is more common in Asian populations (up to 6% in our series).

Epidemiology of thyroid eye disease

TED tends to have a bimodal presentation during the fourth or sixth decade of life. The risk of TED is much higher in patients aged 40-60 years than younger patients. The female-to-male ratio is about 9:1 for all forms of clinical TED and drops to 3:1 for the severe form. In a cohort of 120 Caucasian patients with TED, 90% had Graves' disease, 7% had euthyroid, 3% had Hashimoto thyroiditis, and 1% had primary hypothyroidism.[3] In a multicenter study in Sweden that involved 2916 patients, 20% of hyperthyroid patients suffered from TED at diagnosis.[4] In a Danish study, approximately 5% of patients with Graves' disease developed severe TED.[5]

Chronology of thyroid eye disease

Around 4% of TED patients present more than 6 months and 19% within 6 months *before* the diagnosis of thyroid

dysfunction. About 20% of patients have concurrent ocular and endocrine features at presentation, whereas 22% and 35% develop ocular manifestations within and more than 6 months *after* being treated for thyroid dysfunction, respectively.[3] Over 80% of patients with Graves' hyperthyroidism but no ocular involvement at presentation do not develop TED after the first course (18 months) of antithyroid medications. Mild TED resolves spontaneously in most patients.[6]

Risk factors for thyroid eye disease

The reported risk factors for the development of TED in patients with AITD include male gender, older age (>50 years) at onset, smoking, use of radioactive iodine (RAI), and post-ablative hypothyroidism.[7,8] Compared with non-smokers, smokers have more severe TED, a higher recurrent rate of Graves' disease, are more likely to show progression or occurrence of TED after radioactive iodine, and less responsive to immunosuppressants or orbital radiotherapy.[9] Statin use was shown to have a 40% decreased hazard for TED in a large US cohort,[7] but another study showed possible association of statin use with risk of liver derangement for patients receiving intravenous steroids for active TED.[10]

Clinical features of thyroid eye disease

In a Caucasian cohort, typical signs of TED included eyelid retraction (90%), lid lag (50%), exophthalmos (60%), restrictive myopathy (40%), and optic nerve dysfunction (5%) [**Figure 1**]; only 5% of the cohort had all typical signs (except optic nerve dysfunction).[3] Extraocular features include lid puffiness, lid retraction, lid lag, lagophthalmos

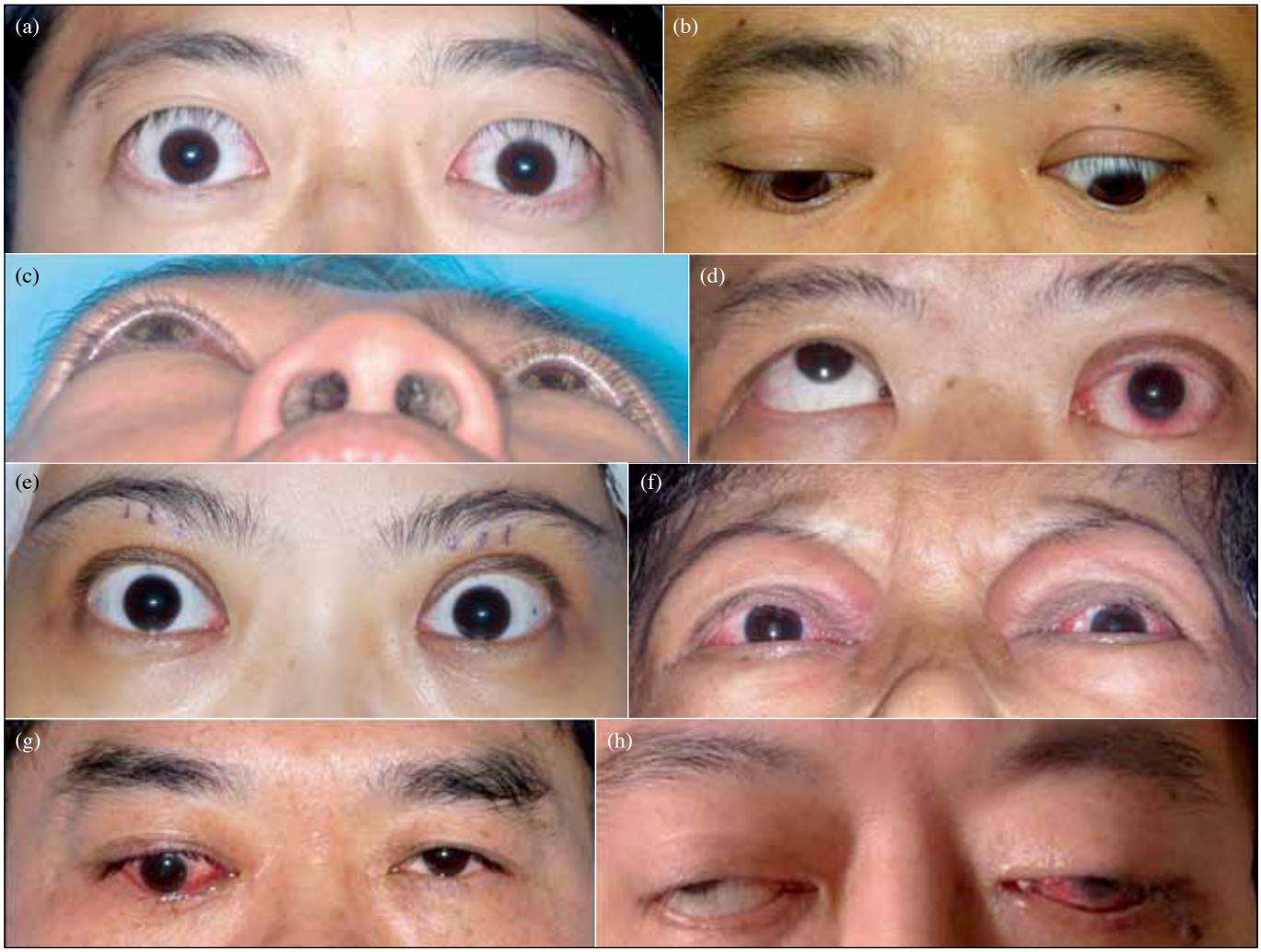

Figure 1. (a) Bilateral upper lid retraction at primary gaze, (b) left upper lid lag on downgaze, (c) asymmetric exophthalmos (more severe on the right) on worm's eye view, (d) severe restrictive myopathy affecting the left eye while attempting upgaze, (e) left dysthyroid optic neuropathy with minimal inflammatory feature or proptosis (visual acuity: right eye: 20/10, left eye: 20/70), (f) symmetric active thyroid eye disease with bilateral upper lid erythema (rare in local population), lid swelling, injection, caruncular swelling (left), chemosis and pain, (g) asymmetric active thyroid eye disease with lid edema and erythema over the right side only, and (h) bilateral lagophthalmos (incomplete eyelid closure) and poor Bell's reflex (the eyes fail to roll up upon lid closure).

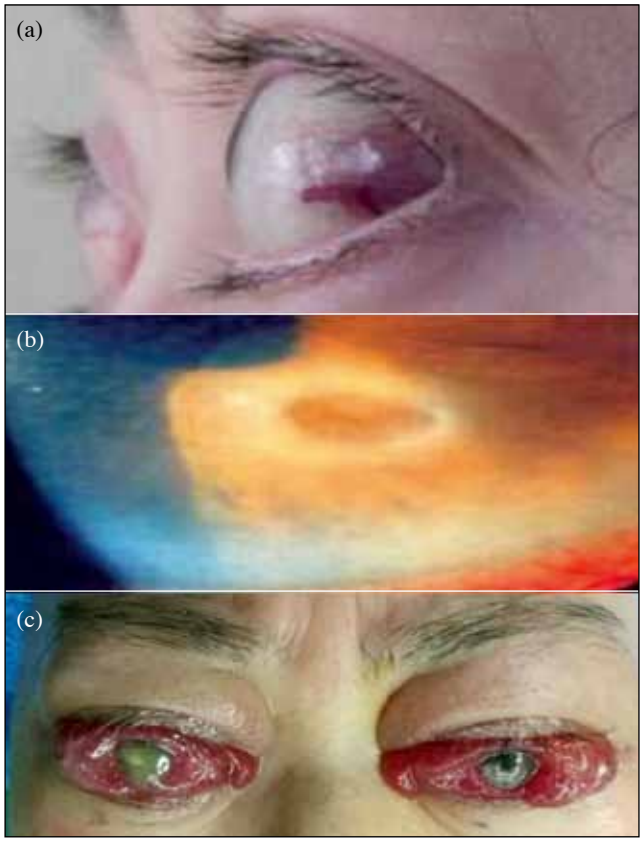

Figure 2. (a) Conjunctival injection around insertion of lateral recti muscles, (b) exposure keratopathy and early microbial keratitis, and (c) severe conjunctival chemosis, injection and bilateral microbial keratitis in a patient with active and untreated thyroid eye disease.

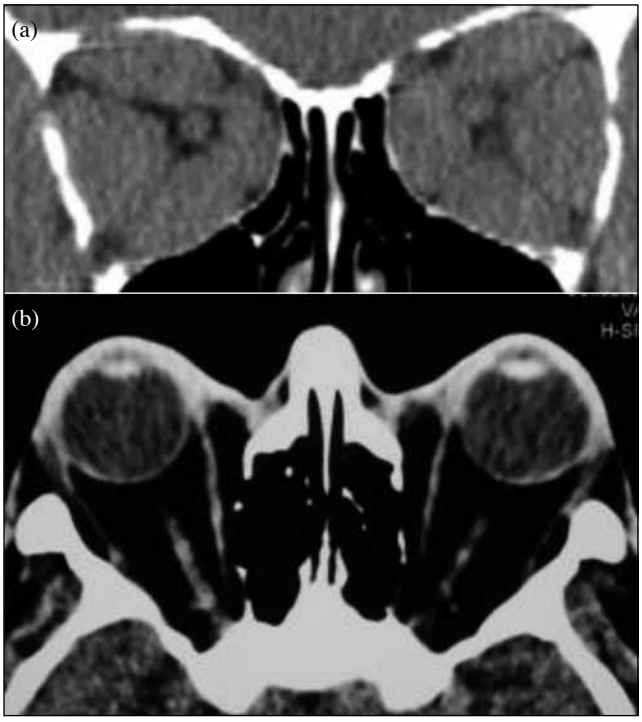

Figure 3. Coronal computed tomography of the orbits showing (a) diffuse and symmetric extraocular muscle enlargement with apical compression on the optic nerve, and (b) symmetrical severe proptosis and straightening of optic nerves with expansion of the orbital fat compartment and minimal muscle involvement in a young female non-smoker with thyroid eye disease.

(incomplete eyelid closure), axial non-pulsatile proptosis (exophthalmos), restrictive strabismus, and acquired lower lid epiblepharon in Asians (**Figure 1**). Intraocular features include conjunctival injection, particularly around the insertion of the rectus muscle, superior limbic keratitis, exposure keratopathy, chemosis, raised intraocular pressure, optic disc swelling, retinal venous congestion, and choroidal folds (**Figure 2**). Vision loss secondary to TED is related to optic nerve dysfunction (dysthyroid optic neuropathy [DON]), exposure keratopathy, uncontrolled intraocular pressure, and globe subluxation.

Proptosis (exophthalmos)

Patients with TED have axial non-pulsatile proptosis (exophthalmos) secondary to orbital venous congestion and enlargement of the extraocular muscles (EOM) due to accumulation of glycosaminoglycan and enhanced adipogenesis. Exophthalmos can be quantified using various types of exophthalmometers (e.g. Hertel) or radiologically with axial orbital scans.

Lid retraction

Lid retraction is the most common sign in TED. The normal upper lid rests at 1-2 mm below the superior limbus (corneal-scleral junction), and the lower lid rests at the inferior limbus. Differential diagnoses of lid retraction include facial paralysis, myasthenia gravis, myotonic dystrophy, Marcus Gunn jaw winking, metabolic disease (uraemia, cirrhosis), Parinaud's (dorsal midbrain) syndrome, Parkinson's disease, contralateral ptosis, and aberrant third nerve regeneration. Lid lag on downgaze, however, is not present from these other causes.

Diplopia

Diplopia or double vision is the most debilitating symptom in TED. Strabismus is restrictive (fibrotic) rather than paralytic in nature. The inferior rectus is most commonly involved, followed by the medial, superior, and lateral rectus. Movement is therefore usually worst in elevation or abduction. Radiologically, the involved EOMs are often enlarged and the tendons are frequently (not exclusively) spared. Fatty deposits within the EOM on computed tomography or T1-weighted magnetic resonance imaging are a specific feature of TED.

Dysthyroid optic neuropathy

DON is thought to be a result of optic nerve compression by the enlarged EOM at the orbital apex (**Figure 3**). In our experience, it may develop in 'cold presenters' with low clinical activity score or minimal proptosis. Postulated mechanisms of DON include inflammation, ischemia or mechanical stretching. Patients may present with horizontal

diplopia with esotropia and abduction deficits secondary to medial rectus enlargement, whereas patients with a fat predominant type of TED may have relatively normal motility but proptosis and stretching of the optic nerve is best shown on sagittal imaging (**Figure 3**). Signs of DON include reduced vision, colour vision, and visual field, presence of afferent papillary defect and optic disc swelling.[11] Patients with existing diabetes or of Asian descent (with shallow orbits) are at higher risk of developing DON. Medical decompression with the use of pulse methylprednisolone (PMP) 750 mg on alternate days x6 over 2 weeks (to avoid consecutive day high dose of 1000 mg and risk of liver dysfunction) may be considered. If response is favorable, orbital radiotherapy can be arranged shortly to prevent recurrence.[11] The rate of compressive optic neuropathy has been reported to be significantly lower in patients who received both orbital radiotherapy and steroids.[12] In our experience, DON could be resolved in selected patients who presented early with pulse steroid, radiotherapy, with or without the use of steroid-sparing agent (double or triple therapies). Nonetheless, if vision remains poor or DON recurs, surgical decompression of the medial wall and/or other walls (depending on the amount of proptosis required) should always be considered.[13]

Thyroid eye disease in Asians

Asian patients often have a delayed and atypical presentation of TED compared with Caucasians. With darker complexion, thicker skin and conjunctival tissues and possibly higher pain threshold, clinical activity score often underestimates or fails to determine deeper orbital involvement. More Asian patients with DON are 'cold-presenters'. Advanced radiological investigation may identify 'subclinical', localized inflammation and justify medical treatment for progressive deformity (e.g. proptosis and diplopia) before rehabilitative surgery. In a Singaporean cohort of 174 patients, corneal erosion secondary to acquired epiblepharon was a common sign in East Asian patients. Mean exophthalmometry values and prevalence of upper eyelid retraction and edema are comparatively lower in East Asian patients.[14]

Thyroid eye disease in paediatric patients

TED is not uncommon in the paediatric population and is usually far less severe than in adults. Among 83 Chinese children aged ≤16 years with Graves' disease, 63% had an ocular presentation: 38.6% had lower lid retraction, 13% had punctate epithelial corneal erosions, 12% had mild proptosis (<3 mm), 1.2% had limited extraocular movement, and none developed visual-threatening complications.[15] In 13 Singaporean children with TED, symptomatic acquired epiblepharon was again more common in those of East-Asian descent (69.2%).[16]

Diagnosis, grading, and investigation of thyroid eye disease

TED is graded separately by severity (tissue remodeling or deformities) and activity (inflammation). The NOSPECS grading (Normal, Only sign, Soft tissue involvement, Proptosis, Extraocular Motility, Corneal exposure, Sight-threatening) is useful to describe the combination of deformities, whereas the clinical activity score measures the degree of inflammation (erythema, swelling, tenderness, loss of function), and the recently proposed VISA (Vision, Inflammation, Strabismus, Appearance) by the International Thyroid Eye Disease Society combines both scales into one.[17]

Diagnosis of TED is still largely clinical, based on a history of autoimmune thyroid disease (Graves' disease more often than Hashimoto thyroiditis) and compatible examination findings. All patients should have appropriate endocrinological evaluation with thyroid function test for serum sensitive thyrotropin and free thyroxine and triiodothyronine levels. Thyroid-related antibodies, specifically thyrotropin receptor antibodies, may be evaluated in patients without a history of thyroid disorder. Other ancillary ocular evaluations include visual field (automated perimetry), colour vision assessment (Ishihara pseudoisochromatic plates), Hess chart (for extraocular movement), and most importantly field of binocular single vision for patients with diplopia.

Orbital imaging is helpful in patients with features of infiltrative TED (motility restriction and/or proptosis), DON, or those awaiting surgical decompression. Non-contrast axial and coronal computed tomography of the orbits readily reveals proptosis, EOM enlargement, apical compressions, and bony anatomical variants for preoperative planning. Nonetheless, it has a limited role in assessing inflammation, as EOM enlargement can be long-standing although retrobulbar fat streakiness can be seen. Diffusion-weighted magnetic resonance imaging is superior to computed tomography in differentiating acute inflammatory from chronically enlarged EOMs and in showing early EOM involvement in 'cold presenters'.[18] Signal intensity ratios on short-tau inversion recovery sequence increase with inflammatory edema and correlate positively with clinical activity score.[19] Signal intensity ratios decrease after PMP and persistently high values post-treatment are associated with treatment failure or recurrence. A prolonged T2 relaxation time is positively correlated with the degree of inflammation and can help to differentiate inflammatory from fibrotic, chronically enlarged EOM and help to identify patients in whom immunosuppressive treatment is appropriate.[20] Orbital scintigraphy, positron emission tomography computed tomography, and digital infrared thermal imaging have been used to measure disease activity with less promising results. The threshold of imaging should be low if atypical features are present.

Differential diagnoses of thyroid eye disease

Differential diagnoses of TED include other orbital disorders such as carotid-cavernous fistula, idiopathic orbital inflammation (pseudotumor), orbital or preseptal

cellulitis, and orbital tumor. Orbital imaging usually can help to differentiate these conditions, and tissue biopsy is sometimes required in patients with euthyroid Graves' ophthalmopathy.

Management of thyroid eye disease

The multidisciplinary approach in managing TED requires collaboration between physicians and ophthalmologists for early diagnosis, triaging, and referral. Treatment consists of symptomatic topical and systemic anti-inflammatory therapies as well as staged surgical rehabilitation.

The management of TED can be summarized as 8S: (1) Stabilization of thyroid function, (2) advice to avoid active and passive Smoking, (3) Staging of disease activity and severity, (4) Symptomatic treatment for dry eye and raised intraocular pressure, (5) Suppression of inflammation during active disease with steroids, radiotherapy, immunosuppressants, and biologics, (6) Staged Surgeries during the inactive phase (orbital decompression, strabismus correction, and eyelid operations), and (7) Surveillance for vision-threatening complications such as DON, severe exposure keratopathy, uncontrolled raised intraocular pressure, and globe subluxation.

Although thyroid status does not always correlate with the presence, severity, or activity of TED, early stabilisation of thyroid function is always recommended. Ophthalmologists are often consulted about the risk of using RAI in patients with Graves' disease. In different studies, up to 15 to 20% of patients who received RAI developed new-onset or worsening of pre-existing TED.[21,22] Patients who are smokers,[22] with unstable thyroid function (raised serum triiodothyronine concentration, or post-RAI uncorrected hypothyroidism) and high levels of thyroid-stimulating immunoglobulin are at risk. RAI is contraindicated in patients with active TED (clinical activity score ≥3/10), which should be managed as above first. Standard dose oral prednisolone prophylaxis (0.4-0.5 mg/kg for 3 months) can be precribed in patients with mild to moderate TED and a high risk of progression, whereas a lower dose (0.2-0.3 mg/kg for 4-6 weeks) is preferred for patients with mild TED or without preexisting TED but with risk factors. Patients without preexisting TED and risk factors do not require glucocorticoid prophylaxis.13,23 RAI presumably causes development or progression of TED by releasing intrathyroidal autoreactive lymphocytes and antigens. Subsequent hypothyroidism (even subclinical) may exacerbate TED due to accumulation of glycosaminoglycans and raised serum thyrotropin. Early and regular biochemical monitoring (every 4-8 weekly) and adequate thyroxine supplementation to prevent post-RAI hypothyroidism are crucial, particularly for those with preexisting TED.

All patients except those with the mildest form of TED benefit from topical lubricants including eye drops and gel during the daytime and thicker ointment at night with or without taping the eyelids closed. Anti-glaucomatous drops may be required to control secondary raised intraocular pressure. Sunglasses may be valuable for those with photophobia or pending surgical rehabilitation. Stick-on (Fresnel) or spectacle-incorporated prism lenses may alleviate a small to moderate degree of diplopia.

Immunosuppressants

Immunosuppressants are indicated for patients with inflammatory orbitopathy with active TED (clinical activity score ≥3/7) and can be considered for those with DON or recent-onset, progressive myopathy. Intravenous PMP has replaced oral prednisolone as the first-line treatment due to fewer side effects and higher effectiveness.[24,25] The European Group on Graves' Orbitopathy (EUGOGO) recommends intravenous 500mg PMP weekly for 6 weeks and then 250 mg for another 6 weeks in patients with moderate-to-severe and active TED.[13] In a randomized double-blind trial that compared cumulative doses of 2.25g, 4.98g, and 7.47g in 12 weekly infusions, more patients achieved improvement in TED with higher cumulative doses (28%, 35%, and 52%, respectively).[26] Nonetheless, major adverse events such as development of diabetes, depression, and severe infection were slightly more frequent in the 7.47g group.[26] Idiosyncratic hepatic failure and arrhythmia can occur at cumulative doses over 8g, although the time period over which this develops has not been specified. A single dose of PMP should not exceed 750mg and consecutive daily therapy should be avoided. Intravenous steroids are contrainidicated in patients with recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular disease or psychiatric disorders. Hypertension and diabetes should be well-controlled before starting steroids. In a review of 14 studies including 1045 TED patients, the morbidity and mortality of intravenous steroid therapy was 6.5% and 0.6%, respectively.[27] Daily oral steroid can be given alternatively for medical or social reasons. Periocular steroid injections, e.g. triamcinolone acetonide (40mg/ml), are useful for asymmetric orbitopathy, mild relapses during tapering, or when the patient is reluctant or systemic steroids are contraindicated. In patients with persistent active disease despite a full cycle of PMP, steroid-sparing agents (e.g. methotrexate, azathioprine, rapamycin, cyclosporine, cyclophosphamide) or newer biologics (e.g. rituximab,[28] adalimumab) may be considered, although high-level evidence is lacking. In a randomized controlled trial to compare rituximab with PMP in 32 patients with moderate-to-severe TED, those who received rituximab achieved a larger decrease in clinical activity score, a lower risk of disease reactivation, and better motility.[29] Nonetheless, another randomized controlled trial to compare rituximab with saline infusion in 21 patients failed to show any additional benefit from rituximab.[30,31]

Orbital radiotherapy

Orbital radiotherapy is a useful adjuvant for patients with steroid-dependent, intolerant or resistant inflammatory orbitopathy, recent-onset progressive myopathy or DON. It consists of fractionated external beam irradiation of 20Gy over ten sessions. Compared with oral steroid therapy,

orbital radiotherapy has comparable effect for moderate to severe orbitopathy and better long-term effect on motility restriction.[12] Combined intravenous PMP plus orbital radiotherapy is more effective than PMP alone.[32] The risk of DON reduces in the combined orbital radiotherapy and steroid group than in the steroid-only group.[12] Orbital radiotherapy is most useful when administered during the course of PMP but is relatively contraindicated in younger (age <30 years) patients or those with diabetic retinopathy. Complications of radiotherapy include dry eyes, cataract (especially when used with concurrent steroid), radiation retinopathy, optic neuropathy, and an increased long-term risk of malignancy.

Selenium supplementation

Selenium supplementation of 100 μg twice daily for 6 months has been shown to improve soft tissue signs and quality of life and prevent progression in patients with recent-onset mild TED.[33] Nonetheless, the study was conducted in selenium-deficient regions and supplementation is beneficial only if serum selenium level is insufficient.[34]

Surgical intervention

Except for patients with vision-threatening complications (DON, globe-subluxation, refractory exposure keratopathy), elective surgery is recommended at least 6 to 9 months after stabilization of endocrine and orbital status. An individualized, staged approach includes orbital decompression, followed by strabismus surgery, correction of lid retraction, and then blepharoplasty and other esthetic surgery.[35]

Common indications for elective orbital decompression include disfiguring proptosis, congestive orbitopathy, and medically uncontrolled exposure keratopathy or raised intraocular pressure. Orbital decompression and/or expansion are broadly classified as bone removal orbital decompression (BROD) or fat removal orbital decompression (FROD). They can be performed in isolation or in combination. BROD differs in the choice of surfaces and incisions for bone removal, e.g. medial (via transcaruncular, transcutaneous Lynch incision or endonasal transethmoidal), inferior (transconjunctival forniceal or swinging eyelid, transcutaneous subciliary or transantral), or lateral orbital walls (transcutaneous upper lid crease, lateral canthal, forniceal or coronal incision). Complications include diplopia, globe dystopia, periorbital sensory changes, orbital hemorrhage, ischemic optic neuropathy, infection, lid malposition, lacrimal gland or lacrimal drainage injury, cerebrospinal fluid leak, and rarely subarachnoid/cerebral hemorrhage.

FROD involves removing intraconal and/or extraconal orbital fat via a transcutaneous (upper lid crease or lower lid subciliary), transconjunctival, and endonasal approach. Fat pockets are usually debulked in the following sequence: inferolateral, superonasal, inferomedial, and superotemporal (to avoid the lacrimal gland and its neurovascular structures). An endoscopic medial wall approach can be used for proptosis reduction as it allows good access to the middle and posterior intraconal fat.[36] FROD may cause fewer cases of new-onset diplopia or worsening of pre-existing diplopia, compared with BROD (for a similar amount of proptosis reduction). Anecdotal experience reports improvement in motility restriction following FROD in selected cases. Orbital hemorrhage and periorbital sensory loss may develop. Very often BROD and FROD are performed in combination in either sequence depending on the surgeon's preference.

Strabismus correction in TED is challenging due to fibrotic EOM and surrounding soft tissue involvement. EOM recession instead of resection is recommended to correct the limited movement rather than the amount of ocular deviation at primary gaze. For example, bilateral asymmetric inferior rectus muscle recession is performed to correct vertical diplopia, to improve upgaze, and to avoid late progressive overcorrection. Detachment of the capsulopalpebral fascia (lower lid retractor) minimizes postoperative lower lid retraction/scleral show. Different techniques have been proposed to improve the outcome of strabismus surgery for patients with TED including an intraoperative relaxed muscle positioning technique, the use of adjustable sutures, operating under monitored anesthetic care or local anesthesia, and simultatneous recession of tenon capsule.

To correct upper lid retraction, mullerotomy, Muller muscle extirpation, levator aponeurosis disinsertion/recession, and levator muscle myotomy with/without the use of adjustable or hangback sutures can be used. Full thickness blepharotomy has gained popularity because of its technical simplicity. Spacers may be required for advanced cases including hard palate/labial mucosal graft, dermis fat/strip graft, auricular/nasal septal cartilage, donor sclera and synthetic materials such as Medpor, Alloderm, aluminium foil, and polytetrafluoroethylene with or without intraoperative anti-metabolites such as mitomycin C and 5-fluorouracil. Transcutaneous/transconjunctival botulinum toxin A, steroid (triamcinolone acetonide) or filler (Restylane) injections have been used to alleviate lagophthalmos and exposure keratopathy before surgical intervention. In cases of severe corneal breakdown, tarsorrhaphy, gluing or corneal graft may be necessary.

Prognosis of thyroid eye disease

After achieving euthyroidism, up to 90% of lid retraction and 30% of restrictive myopathy improve, but proptosis rarely improves.[37] For patients with clinically evident TED (NOSPECS class 3 or above), the typical disease course continues for 18 to 36 months before it stabilizes.

Prevention of thyroid eye disease

Although the etiology/pathogenesis of Graves' disease/TED remains unknown, subjects at risk (family or personal history of autoimmune thyroid diseases, autoantibodies or

biochemical dysthyroidism) are advised to quit active and to avoid passive smoking (primary prevention to avoid occurrence).[37] Secondary prevention to avoid progression of subclinical TED involves early and tight control of dysthyroidism (in particular avoiding post-ablative hypothyroidism). Tertiary prevention to avoid development of vision-threatening complications requires early and judicious use of immunosuppressive therapies, orbital irradiation, and timely surgical rehabilitation.

The first thyroid eye clinic in Hong Kong

The first thyroid eye clinic in Hong Kong was established in fall 2010, and nearly 700 TED patients were managed in the past 6 years. Among them, 103 and 174 patients received oral and intravenous steroid, respectively. 77 required steroid-sparing agents (methotrexate or azathioprine) and 148 underwent orbital radiotherapy during systemic steroid treatment. 333 computed tomographies and 268 magnetic resonance imaging of the orbits were reviewed. 113 eyes were operated for orbital decompression in isolation or combination using transconjunctival fat removal (n=29), medial wall bone removal (n=63, 50 through the endoscopic transethmoidal approach), or lateral wall bone removal (n=79, 6 through the transforniceal conjunctival approach). We considered that the resource and research implication of TED in Hong Kong have been grossly underestimated.

Conclusion

TED is the most common cause of proptosis or lid retraction in adults and can present asymmetrically. At presentation, one in five patients with TED has normal thyroid function. Smoking cessation and early stabilisation of thyroid function are the most important primary and secondary TED prevention measure. Although most TED patients can be managed conservatively, patients with active, progressive or severe disease warrant specialist evaluation and consideration of treatment with intravenous steroid, orbital radiotherapy, and/or surgical decompression. More than one operation may be required to correct established or iatrogenic deformities.

References

1. *Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362:726-38.*
2. *Yeatts RP. Quality of life in patients with Graves ophthalmopathy. Trans Am Ophthalmol Soc. 2005;103:368-411.*
3. *Bartley GB, Fatourechi V, Kadrmas EF, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol. 1996;121:284-90.*
4. *Abraham-Nordling M, Bystrom K, Torring O, et al. Incidence of hyperthyroidism in Sweden. Eur J Endocrinol. 2011;165:899-905.*
5. *Laurberg P, Berman DC, Bulow Pedersen I, Andersen S, Carle A. Incidence and clinical presentation of moderate to severe graves' orbitopathy in a Danish population before and after iodine fortification of salt. J Clin Endocrinol Metab. 2012;97:2325-32.*
6. *Tanda ML, Piantanida E, Liparulo L, et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. J Clin Endocrinol Metab. 2013;98:1443-9.*
7. *Stein JD, Childers D, Gupta S, et al. Risk factors for developing thyroid-associated ophthalmopathy among individuals with Graves disease. JAMA Ophthalmol. 2015;133:290-6.*
8. *Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. Thyroid. 2010;20:777-83.*
9. *Wiersinga WM. Smoking and thyroid. Clin Endocrinol (Oxf). 2013;79:145-51.*
10. *Covelli D, Vannucchi G, Campi I, et al. Statins may increase the risk of liver dysfunction in patients treated with steroids for active graves' orbitopathy. J Clin Endocrinol Metab. 2015;100:1731-7.*
11. *McKeag D, Lane C, Lazarus JH, et al. Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. Br J Ophthalmol. 2007;91:455-8.*
12. *Shams PN, Ma R, Pickles T, Rootman J, Dolman PJ. Reduced risk of compressive optic neuropathy using orbital radiotherapy in patients with active thyroid eye disease. Am J Ophthalmol. 2014;157:1299-305.*
13. *Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5:9-26.*
14. *Lim NC, Sundar G, Amrith S, Lee KO. Thyroid eye disease: a Southeast Asian experience. Br J Ophthalmol. 2015;99:512-8.*
15. *Chan W, Wong GW, Fan DS, Cheng AC, Lam DS, Ng JS. Ophthalmopathy in childhood Graves' disease. Br J Ophthalmol. 2002;86:740-2.*
16. *Lim NC, Amrith S, Sundar G. Pediatric thyroid eye disease--the Singapore experience. Orbit. 2014;33:96-103.*
17. *Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997;47:9-14.*
18. *Politi LS, Godi C, Cammarata G, et al. Magnetic resonance imaging with diffusion-weighted imaging in the evaluation of thyroid-associated orbitopathy: getting below the tip of the iceberg. Eur Radiol. 2014;24:1118-26.*
19. *Higashiyama T, Nishida Y, Morino K, et al. Use of MRI signal intensity of extraocular muscles to evaluate methylprednisolone pulse therapy in thyroid-associated ophthalmopathy. Jpn J Ophthalmol. 2015;59:124-30.*
20. *Tachibana S, Murakami T, Noguchi H, et al. Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for Graves' ophthalmopathy. Endocr J. 2010;57:853-61.*
21. *Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham*

P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf). 2008;69:943-50.

22. *Stan MN, Durski JM, Brito JP, Bhagra S, Thapa P, Bahn RS. Cohort study on radioactive iodine-induced hypothyroidism: implications for Graves' ophthalmopathy and optimal timing for thyroid hormone assessment. Thyroid. 2013;23:620-5.*
23. *Shiber S, Stiebel-Kalish H, Shimon I, Grossman A, Robenshtok E. Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis. Thyroid. 2014;24:1515-23.*
24. *Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. J Clin Endocrinol Metab. 2009;94:2708-16.*
25. *Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005;90:5234-40.*
26. *Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012;97:4454-63.*
27. *Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab. 2011;96:320-32.*
28. *Khanna D, Chong KK, Afifiyan NF, et al. Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy. Ophthalmology. 2010;117:133-9.*
29. *Salvi M, Vannucchi G, Curro N, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015;100:422-31.*
30. *Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab. 2015;100:432-41.*
31. *Wiersinga WM. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. Lancet Diabetes Endocrinol. 2017;5:134-42.*
32. *Kim JW, Han SH, Son BJ, Rim TH, Keum KC, Yoon JS. Efficacy of combined orbital radiation and systemic steroids in the management of Graves' orbitopathy. Graefes Arch Clin Exp Ophthalmol. 2016;254:991-8.*
33. *Marcocci C, Kahaly GJ, Krassas GE, et al. Selenium and the course of mild Graves' orbitopathy. N Engl J Med. 2011;364:1920-31.*
34. *Dharmasena A. Selenium supplementation in thyroid associated ophthalmopathy: an update. Int J Ophthalmol. 2014;7:365-75.*
35. *Goldberg RA. Advances in surgical rehabilitation in thyroid eye disease. Thyroid. 2008;18:989-95.*
36. *Wu W, Selva D, Bian Y, et al. Endoscopic medial orbital fat decompression for proptosis in type 1 graves orbitopathy. Am J Ophthalmol. 2015;159:277-84.*
37. *Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. Thyroid. 2002;12:855-60.*

Review Article

Small incision lenticule extraction: a review

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Abstract

Small incision lenticule extraction (SMILE) is a new type of keratorefractive surgery and is gaining popularity in Hong Kong and worldwide. This article aims to provide a brief introduction to SMILE, including the surgical steps, common intraoperative difficulties, and a literature review on its visual, refractive, and safety outcomes.

Key words: Myopia; Refractive surgical procedures

Introduction

The increased prevalence of myopia has increased the demand for refractive surgery to correct myopia. Small incision lenticule extraction (SMILE) has gained popularity since its first prospective study in 2010.[1] This article aims to give an overview of the SMILE procedure, highlight some intraoperative tips, discuss its advantages and limitations, and review the literature about its efficacy and safety.

Evolution of refractive surgery

Laser-assisted *in-situ* keratomileusis (LASIK) has been the most popular method of keratorefractive surgery in the past decade. It involves creation of a corneal flap, followed by stromal ablation with excimer laser. It has proven safety, visual, and refractive outcomes with almost immediate visual recovery. Nonetheless, creation of the flap is associated with the risk of early flap-related complications and post-LASIK dry eyes. The procedure also weakens the biomechanical strength of the cornea and may lead to late complications including regression and postoperative ectasia.

Femtosecond laser and related techniques

Femtosecond laser is characterized by ultrafast pulses of light at a duration of 10^{-15} seconds. A laser beam is focused at a precise depth within the cornea. At the point of focus, brief bursts of energy convert the local tissue into a plasma state, vaporizing a small volume of tissue. This process is called photodisruption. Femtosecond laser creates a tissue plane with extremely limited collateral damage.[2] The use of femtosecond laser in refractive surgery has gone through different generations.[3] It was first used in LASIK flap creation in replacement of microkeratome, giving rise to femtosecond laser-assisted LASIK. With further development, stromal ablation is avoided, and instead an intrastromal lenticule is cut and removed from the cornea. This is known collectively as refractive lenticule extraction. The first to emerge was femotosecond lenticule extraction (FLEX). It involved creating a corneal flap and an intrastromal lenticule using a femtosecond laser. The lenticule was then extracted after lifting the corneal flap. Later on, SMILE was developed in which the lenticule was extracted via a small arcuate incision without the need for a corneal flap.

SMILE procedure

SMILE distinguishes itself from LASIK by avoiding the need to create a flap. In essence, it involves creation of an intrastromal lenticule and peripheral incisions using

femtosecond laser, followed by dissection and removal of the stromal lenticule (**Figure**).

Docking and femtosecond laser incisions

The first step of SMILE femtosecond laser is docking and incision. Achieving an accurate centration of the eye is quintessential to the success of SMILE. The eye is placed under the laser platform and the curved contact glass, and the surgeon looks at the eye via a surgical microscope. A green indicator light can be seen via the microscope and should be placed at the centre of the pupil. To ensure proper centration, the patient fixates on an internal target light coming from the treatment pack, while the surgeon adjusts the position of the operative table and hence the patient's eye, a process termed docking. The surgeon then moves the table up so that the cornea is partly applanated onto the contact glass. Once the centration is confirmed, the surgeon applies negative suction to keep the eye in place. Femtosecond incisions can then be initiated.

Creation of intrastromal lenticule

There are four femtosecond laser incisions that create the intralamellar lenticule. The first incision creates the posterior plane of the lenticule. The laser passes from the periphery to the center in a spiral fashion, a maneuver that minimizes the time during which the central cornea is affected. The second incision creates the side-cut at 90° perpendicular to the anterior cap along its periphery. The third incision creates the anterior cap of the lenticule by passing the laser from the center to the periphery in a spiral manner, completing the carving of the intralamellar lenticule. The fourth incision is a small incision of 2 to 5mm along the circumference of the anterior cap to enable extraction of the lenticule.

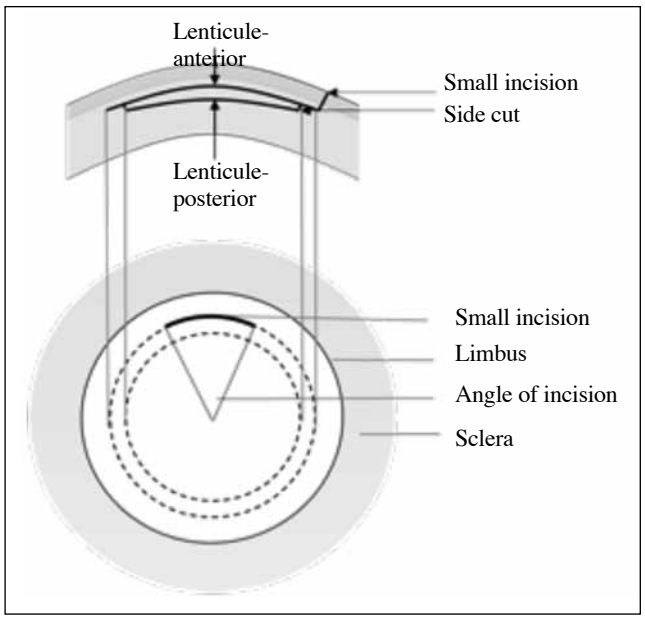

Figure. Schematic diagram illustrating small incision lenticule extraction.

The technical parameters for these laser-generated incisions have not been standardized. Based on our clinical experience, we recommend a cap thickness of 120 μm, cap diameter of 7.5 mm, lenticule diameter of 6.5 mm with a transition zone of 0.1 mm, cut energy of 1.4 nJ, and spot and tracking distance of 2.0-3.0 μm.[4]

Manual extraction of the lenticule

Following the femtosecond laser incisions, the suction to keep the eye in place can be removed, and the stromal lenticule is ready to be extracted. The surgeon inserts a spatula into the side-cut to dissect residual lenticular appendages along the anterior plane and then the posterior plane. When the anterior plane is dissected, the edge of the posterior surface cannot be seen; the contrary is true when the posterior plane is dissected. This difference in appearance helps the surgeon to ensure dissection at the correct surface. Once the dissection is completed and no appendages are left, the lenticule can be extracted with a pair of forceps. A segment of residual corneal tissue anterior to the lenticule becomes largely disconnected from the remainder of the cornea; this segment is known as the cap. Care should be taken not to damage it. Some surgeons may irrigate the intralamellar space, some not. Finally the edge of the side-cut is repositioned with a brush.

Postoperatively, topical steroid, antibiotics, and lubricating eyedrops are prescribed for several weeks.

Indications and contraindications

SMILE is appropriate for most patients who are fit for refractive corneal surgeries. Its use in correcting myopia and myopic astigmatism has been established.[5-7] Based on our experience, the optimal range of spherical and cylinder is -0.75 D to -10 D and < -5 D, respectively. Keratometry should fall within 38-48 D. Nonetheless, its applicability in correcting hypermetropia remains to be investigated. Other inclusion criteria include age 18 years or above, stable refraction, transparent cornea with no history of keratitis or scar, normal topography, and corneal thickness > 480 μm. SMILE is contraindicated in those with previous intraocular surgery, ocular co-morbidities or autoimmune connective tissue disorders.

Common difficulties for surgeons

Many refractive surgeons experienced with LASIK may hesitate to switch to SMILE due to the learning curve. We discuss a few common intraoperative difficulties and provide some management tips.

Maintaining centration

Without proper centration, the accuracy of laser-based incisions is compromised. To achieve better centration during docking, the patient should be instructed to keep fixating on the light until suction is applied. Patients with more severe astigmatism or a larger angle Kappa may need further adjustment. Negative suction maintains the eye position

once centration is achieved. The strength of suction needs to be carefully adjusted; a lower suction allows the patient to fixate on the light throughout the procedure. The size of the suction ring depends on the size of the globe and baseline refractive error. In general, a small ring size is recommended for myopia correction in Chinese, whereas a medium ring size can be used for astigmatism correction. The connecting tubes should be placed at the patient's temporal side. Suction loss may occur even when suction is properly achieved in the first instance. To prevent this, the surgeon should avoid putting the conjunctiva under suction. Excess liquid and conjunctival discharge should be wiped away in time, and environmental interference minimized. In case instability is noticed, the surgeon should re-apply suction. If suction loss occurs, the surgeon can choose to continue with SMILE, convert to LASIK or FLEX, or reschedule the operation.

Locating and extracting the lenticule

Locating the lenticule is readily achievable when the following steps are attended to. The lenticule should not be too thin. Blunt instruments should be used to dissect the lenticule from within the cornea, first along the periphery of the anterior surface. The surgeon should search for the edge of the lenticule using the gas bubble as a guide. The side cuts should be carefully identified. Should the lenticule not be extracted, the surgeon can use a shorter and sharper instrument to accurately identify the edge. Slit lamp or anterior segment optical coherence tomography may be used in difficult cases. If lenticular extraction remains non-feasible despite extensive searching, the incisions need to be closed and the operation rescheduled. Alternatively, the surgeon can convert to the FLEX procedure.

The lenticule may be difficult to extract if it is not properly created. This may arise from incorrect setting of laser parameters, incomplete side cut, or unstable laser performance. Either too high or too low energy is problematic; in the former, an opaque bubble layer forms in the cornea, whereas in the latter the spot distance and track distance increase. Whatever the cause, difficulty in extraction can be overcome using careful blunt dissection. Laser parameters should be adjusted to produce useful cuts. Incomplete side cuts can be managed using scissors or special equipment.

During its extraction, the lenticule may be torn or left behind, causing residual lenticular tissue. This may occur when the cornea has a pre-existing defect, such as scarring, when laser energy was inappropriately high causing an opaque bubble layer around the lenticule or when the lenticule is too thin or when the patient is not cooperative. To prevent these, patients with corneal scars should be screened out during a preoperative assessment. In those with low refraction, the cap thickness should be increased. Gentle maneuvers to ensure complete clearance of the anterior and posterior lamellar plane are essential. The lenticule should be gently grasped with forceps. Should tearing occur, a careful dissection should be performed. All residual lenticular tissue should be removed. Small strips of tissue at the periphery may be observed, but those in the optical zone must be removed.

Cap perforation or abrasion at the side-cut incision can be problematic. The risk is higher when the cap is too thin or when the side-cut is too small. Gentle surgical technique and correct choice of instruments can prevent this, as well as ensuring the patient does not move the eye suddenly. Mild tears can be observed, but obvious tears need to be apposed to prevent epithelial ingrowth, which is readily achieved using a bandage contact lens.

Efficacy and safety

The efficacy of SMILE is defined by the percentage of eyes with good postoperative uncorrected distant visual acuity (UDVA).[8,9] In one SMILE study, 62% of eyes achieved UDVA ≥ 20/20, whereas 93% achieved ≥ 20/40.[8] The corresponding percentages for LASIK were 71% and 95%. In a study comparing SMILE with LASIK for 111 eyes, the two cohorts did not differ significantly in percentage of eyes with an UDVA of 20/20 or better at 1 and 3 months.[10] In addition, higher order aberrations and spherical aberrations were significantly lower in the SMILE cohort.[10] In terms of safety, most patients could maintain corrected distance visual acuity (CDVA), with a safety index (defined as postoperative CDVA / preoperative CDVA) between 1.0 and 1.1.[8,11] A loss of two lines or more was noted in only 0-2.3% of SMILE patients, compared with 0-2.4% for LASIK. High order aberrations and spherical aberrations were less common following SMILE than LASIK.[10,12-14] This was postulated to be related to the lack of flap creation in SMILE, as well as a more favorable healing response with femtosecond laser than with excimer laser.

With SMILE, a predictable correction in refractive outcome can be achieved. 79 to 92% of patients achieved within ± 0.5D of target refraction, compared with 80 to 90% for LASIK. For both procedures, >90% subjects could achieve within ± 1.0D of target refraction.[8,9] Refractive outcome was stable in long-term follow-up. Over 5 years, a regression of 0.48D was noted in SMILE patients, compared with 0.63-0.97D in LASIK patients.[15]

SMILE is proposed to cause less dry eye symptoms by preserving corneal sensation in the absence of flap creation. Evidence suggests that SMILE is associated with less denervation, accelerated healing of the ocular surface, and better corneal sensitivity.[16-19] Higher percentages of LASIK than SMILE patients are reported to have mild to moderate dry eyes 6 months postoperatively.[20]

Biomechanical stability is postulated to be stronger with SMILE, owing to preservation of the anterior corneal stroma. Mathematical modelling suggests that stromal tensile strength should be stronger with SMILE than LASIK.[21] Nonetheless, clinical results measured with Ocular Response Analyzer or CorVisST remain controversial.[9,22-26] A biomechanically stronger cornea should translate into less

regression and risk of ectasia in the long-term, although no such long-term data is available for SMILE yet.

A meta-analysis of 11 comparative studies involving 1101 eyes provides more insight into the efficacy and safety of SMILE in comparison with FS-LASIK.[27] The two procedures did not differ significantly in the mean postoperative refractive standard error, proportion of eyes losing one or more lines of CDVA, proportion of eyes achieving UDVA 20/20 or better, or proportion of eyes with postoperative refractions within ± 1.0 D of the target. At 6 months postoperatively, the SMILE group had significantly higher corneal sensitivity and longer tear break-up time. These results were in line with the impression derived from the findings of individual studies that SMILE and FS-LASIK were comparable in terms of safety and efficacy, with SMILE potentially superior in reducing dry eye symptoms.

We have also reported comparable efficacy and safety with SMILE.[4,28] For efficacy, UDVA was 20/20 or better in 48 to 80% of all subjects, and 20/40 or better in 93 to 100%. For safety, no patient had a loss of two or more lines of CDVA, and 93 to 99% had no loss of CDVA. For predictability, 94% achieved within ± 1.0D of target refraction. Correction of astigmatism was often inadequate in SMILE.[29,30] Our data showed that 87 to 96% of all subjects had correction of astigmatism within ±0.5D. Using vector analysis, we quantified a correction index of astigmatism by comparing surgical with target-induced astigmatism. The index was 0.81-1.00 for SMILE and 0.94-1.03 for LASIK, suggesting satisfactory correction of astigmatism for both procedures.[4,31] In terms of biomechanical stability, our experience suggests less reduction in corneal hysteresis, corneal resistance factor in SMILE.[26] We also observed a learning curve in our SMILE cases (unpublished data).

The most common complications of SMILE, in descending order, were peripheral corneal abrasion (5.5%), corneal haze (5.4%), early dry eye (3.2%), lenticule extraction difficulties (1.5%), tear at incision edge (1.5%), suction loss (1.0%), epithelial ingrowth (0.5%), irregular topography (0.5%), corneal microstriae (0.4%), and keratitis (0.3%).[29]

Conclusion

SMILE has good safety and efficacy comparable with LASIK. As a flapless procedure, it preserves more corneal sensation than LASIK and results in less postoperative dry eyes. It also has biomechanical advantages, although this remains to be proven in studies with longer follow-up and larger sample size.

References

1. *Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol. 2011;95:335-9.*
2. *Trikha S, Turnbull AM, Morris RJ, Anderson DF, Hossain P. The journey to femtosecond laser-assisted cataract surgery: new beginnings or a false dawn? Eye (Lond). 2013;27:461-73.*
3. *Ang M, Mehta JS, Chan C, Htoon HM, Koh JC, Tan DT. Refractive lenticule extraction: transition and comparison of 3 surgical techniques. J Cataract Refract Surg. 2014;40:1415-24.*
4. *Chan TC, Ng AL, Cheng GP, et al. Vector analysis of astigmatic correction after small-incision lenticule extraction and femtosecond-assisted LASIK for low to moderate myopic astigmatism. Br J Ophthalmol. 2016;100:553-9.*
5. *Liu M, Chen Y, Wang D, et al. Clinical outcomes after SMILE and femtosecond laser-assisted LASIK for myopia and myopic astigmatism: a prospective randomized comparative study. Cornea. 2016;35:210-6.*
6. *Hansen RS, Lyhne N, Grauslund J, Vestergaard AH. Small-incision lenticule extraction (SMILE): outcomes of 722 eyes treated for myopia and myopic astigmatism. Graefes Arch Clin Exp Ophthalmol. 2016;254:399-405.*
7. *Güell JL, Verdaguer P, Mateu-Figueras G, et al. SMILE procedures with four different cap thicknesses for the correction of myopia and myopic astigmatism. J Refract Surg. 2015;31:580-5.*
8. *Moshirfar M, McCaughey MV, Reinstein DZ, Shah R, Santiago-Caban L, Fenzl CR. Small-incision lenticule extraction. J Cataract Refract Surg. 2015;41:652-65.*
9. *Reinstein DZ, Archer TJ, Gobbe M. Small incision lenticule extraction (SMILE) history, fundamentals of a new refractive surgery technique and clinical outcomes. Eye Vis (Lond). 2014;1:3.*
10. *Lin F, Xu Y, Yang Y. Comparison of the visual results after SMILE and femtosecond laser-assisted LASIK for myopia. J Refract Surg. 2014;30:248-54.*
11. *Shortt AJ, Allan BD, Evans JR. Laser-assisted in-situ keratomileusis (LASIK) versus photorefractive keratectomy (PRK) for myopia. Cochrane Database Syst Rev. 2013;1:CD005135.*
12. *Agca A, Demirok A, Cankaya KI, et al. Comparison of visual acuity and higher-order aberrations after femtosecond lenticule extraction and small-incision lenticule extraction. Cont Lens Anterior Eye. 2014;37:292-6.*
13. *Tran DB, Sarayba MA, Bor Z, et al. Randomized prospective clinical study comparing induced aberrations with IntraLase and Hansatome flap creation in fellow eyes: potential impact on wavefront-guided laser in situ keratomileusis. J Cataract Refract Surg. 2005;31:97-105.*
14. *Wei S, Wang Y, Wu D, Zu P, Zhang H, Su X. Ultrastructural changes and corneal wound healing after SMILE and PRK procedures. Curr Eye Res. 2016;41:1316-25.*
15. *Blum M, Täubig K, Gruhn C, Sekundo W, Kunert KS. Five-year results of small incision lenticule extraction (ReLEx SMILE). Br J Ophthalmol. 2016;100:1192-5.*
16. *Mohamed-Noriega K, Riau AK, Lwin NC, Chaurasia SS, Tan DT, Mehta JS. Early corneal nerve damage and recovery following small incision lenticule extraction (SMILE) and*

laser in situ keratomileusis (LASIK). Invest Ophthalmol Vis Sci. 2014;55:1823-34.

17. Wei S, Wang Y. Comparison of corneal sensitivity between FS-LASIK and femtosecond lenticule extraction (ReLEx flex) or small-incision lenticule extraction (ReLEx smile) for myopic eyes. Graefes Arch Clin Exp Ophthalmol. 2013;251:1645-54.
18. Xu Y, Yang Y. Dry eye after small incision lenticule extraction and LASIK for myopia. J Refract Surg. 2014;30:186-90.
19. Li M, Zhao J, Shen Y, et al. Comparison of dry eye and corneal sensitivity between small incision lenticule extraction and femtosecond LASIK for myopia. PLoS One. 2013;8:e77797.
20. Denoyer A, Landman E, Trinh L, Faure JF, Auclin F, Baudouin C. Dry eye disease after refractive surgery: comparative outcomes of small incision lenticule extraction versus LASIK. Ophthalmology. 2015;122:669-76.
21. Sinha Roy A, Dupps WJ Jr, Roberts CJ. Comparison of biomechanical effects of small-incision lenticule extraction and laser in situ keratomileusis: finite-element analysis. J Cataract Refract Surg. 2014;40:971-80.
22. Shen Y, Chen Z, Knorz MC, Li M, Zhao J, Zhou X. Comparison of corneal deformation parameters after SMILE, LASEK, and femtosecond laser-assisted LASIK. J Refract Surg. 2014;30:310-8.
23. Pedersen IB, Bak-Nielsen S, Vestergaard AH, Ivarsen A, Hjortdal J. Corneal biomechanical properties after LASIK, ReLEx flex, and ReLEx smile by Scheimpflug-based dynamic tonometry. Graefes Arch Clin Exp Ophthalmol. 2014;252:1329-35.
24. Vestergaard AH, Grauslund J, Ivarsen AR, Hjortdal JO. Central corneal sublayer pachymetry and biomechanical properties after refractive femtosecond lenticule extraction. J Refract Surg. 2014;30:102-8.
25. Wang D, Liu M, Chen Y, et al. Differences in the corneal biomechanical changes after SMILE and LASIK. J Refract Surg. 2014;30:702-7.
26. Wu D, Wang Y, Zhang L, Wei S, Tang X. Corneal biomechanical effects: small-incision lenticule extraction versus femtosecond laser-assisted laser in situ keratomileusis. J Cataract Refract Surg. 2014;40:954-62.
27. Zhang Y, Shen Q, Jia Y, Zhou D, Zhou J. Clinical outcomes of SMILE and FS-LASIK used to treat myopia: a meta-analysis. J Refract Surg. 2016;32:256-65.
28. Zhang J, Wang Y, Wu W, Xu L, Li X, Dou R. Vector analysis of low to moderate astigmatism with small incision lenticule extraction (SMILE): results of a 1-year follow-up. BMC Ophthalmol. 2015;15:8.
29. Ivarsen A, Asp S, Hjortdal J. Safety and complications of more than 1500 small-incision lenticule extraction procedures. Ophthalmology. 2014;121:822-8.
30. Zhang J, Wang Y, Wu W, Xu L, Li X, Dou R. Vector analysis of low to moderate astigmatism with small incision lenticule extraction (SMILE): results of a 1-year follow-up. BMC Ophthalmol. 2015;15:8.
31. Zhang J, Wang Y, Chen X. Comparison of moderate- to high-astigmatism corrections using wavefront-guided laser in situ keratomileusis and small-incision lenticule extraction. Cornea. 2016;35:523-30.

ORIGINAL ARTICLE

Intravitreal bevacizumab versus triamcinolone acetonide for uveitic cystoid macular edema: a meta-analysis

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Abstract

Purpose: To carry out a meta-analysis of studies comparing intravitreal bevacizumab (IVB) with intravitreal triamcinolone acetonide (IVT) in the treatment of uveitic cystoid macular edema.
Methods: Relevant publications were identified through PubMed, EMBASE, and the Cochrance Controlled Trials Register. Patients prescribed IVB verus IVT were compared in terms of central macular thickness (CMT) and best-corrected visual acuity (BCVA) at baseline and 1, 3, and 6 months after treatment.
Results: Four comparative studies with 72 eyes in the IVB group and 76 eyes in the IVT group were included. Funnel plots, the Egger method, and Begg method did not show any publication bias. The IVT and IVB groups were comparable in BCVA at 1 month (weighted mean deviation [WMD] = 0.06, 95% confidence interval [CI] = -0.05-0.16, p = 0.31), 3 months (WMD = 0.09, 95% CI= -0.01-0.18, p = 0.08), and 6 months (WMD = 0.04, 95% CI = -0.02-0.11, p = 0.20), as well as change in CMT at one month (WMD = 5.17, 95% CI = -9.2-19.5, p = 0.48) and 3 months (WMD = 43.3, 95% CI = -11.6-98.2, p = 0.12). At 6 months, change in CMT was higher in the IVT than IVB group (WMD = 40.6, 95% CI = 8.2-73.0, p = 0.01).
Conclusion: At 6 months after injection, IVT was more effective than IVB in reducing CMT.

Key words: Bevacizumab; Macular edema; Meta-analysis; Triamcinolone acetonide; Uveitis

Introduction

Uveitis is an etiologically heterogeneous disease characterized by inflammation of the iris, ciliary body or choroid. It can lead to a loss in visual acuity, usually due to cystoid macular edema.[1-4] Cystoid macular edema is usually treated with topical application of non-steroidal anti-inflammatory drugs or steroidal drugs and, if not sufficient, systemic application of anti-inflammatory medication.[5] Intravitreal triamcinolone acetonide (IVT) and intravitreal bevacizumab (IVB) have been applied in patients with uveitic cystoid macular edema resistant to topical medication.[6-13] Indication for use of anti-vascular endothelial

growth factor (VEGF) drugs for uveitis macular edema was elevated intraocular concentration of VEGF.[14] Triamcinolone counteracts VEGF in a non-specific way, whereas anti-VEGF drugs as antibodies with a high specificity neutralize the effect of VEGF.

Triamcinolone and bevacizumab differ in their pharmacokinetic properties and side effects. This study aimed to carry out a meta-analysis of studies that compared IVT with IBV in terms of their efficacy and side effects in the treatment of uveitic cystoid macular edema.

Methods

This study was approved by the ethics committee of the Beijing Chaoyang Hospital, Capital Medical University. Patient consent was not required. Electronic databases of PubMed, EMBASE, and Cochrane Controlled Trials Register were searched for studies up to November 30, 2016, using key words 'bevacizumab', 'triamcinolone acetonide', 'avastin', and 'uveitic cystoid macular edema'. References were also searched for relevant articles. There was no language restriction.

Inclusion criteria were (1) randomized controlled trials and high-quality comparative studies comparing IVB with IVT for cystoid macular edema; and (2) availability of data on age, gender, refractive error, history of disease, best-corrected visual acuity (BCVA), and central macular thickness (CMT); and (3) number of patients >20. Exclusion criteria were (1) IVB or IVT was not the only treatment or the efficacy of the treatment was not determined; (2) study design involved inappropriate randomization or insufficient information about the study population or clear definition of the disease; and (3) repeated publication; for articles published by the same groups of authors, only the earliest or those with the largest data volume were used.

Data extracted included (1) title, author, publication data, study site; (2) number of patients, age, dosage of the drugs applied, number of intravitreal injections, and follow-up duration; and (3) BCVA and CMT.

The meta-analysis was carried out using the Cochrane Review Manager (RevMan; version 5.0 software). The treatment effect was estimated by means of weighted mean deviation (WMD) of BCVA and CMT. 95% confidence intervals (CI) were presented. Random effects models were used, taking into account the possibility of heterogeneity between studies (tested by the Z test). A p value <0.05 was considered statistically significant. Publication bias was assessed using a funnel plot, Egger´s linear regression method, and the Begg rank correlation test.

Results

A total of 43 articles were identified; 39 were excluded and the remaining four were reviewed.[15-18] The allocation to the IVB or IVT group was randomized; the sample size ranged from 21 to 60 eyes; and follow-up ranged from 6 to 9 months (**Table 1**). There were 72 eyes in the IVB group and 76 eyes in IVT group. The two groups did not differ significantly in age, gender, refractive error, baseline BCVA and CMT, or disease duration. No patients had a systemic disorder that may have caused the uveitis or an ocular disease other than that causing uveitis. Patients with a history of other diseases causing macular edema (such as diabetes mellitus and retinal vein occlusions) were excluded. All patients had undergone a detailed ophthalmological examination, including assessment of BCVA, a fundus examination with the pupils medically dilated, color fundus photography, fluorescein angiography, indocyanine green angiography, and optical coherence tomography of the retina.

All four studies reported BCVA at 1, 3, and 6 months after initial treatment; the values were converted to the logarithm of the minimum angle of resolution (logMAR) and were summarized by means of meta-analysis of I^2 = 50%, 78%, and 79%, respectively. The two groups did not differ significantly in BCVA at 1 month (WMD = 0.06, 95% CI = -0.05-0.16, p = 0.31), 3 months (WMD = 0.09, 95% CI = -0.01-0.18, p = 0.08), or 6 months (WMD = 0.04, 95% CI = -0.02-0.11, p = 0.20) [**Table 2**].

All four studies reported CMT at 1, 3, and 6 months after

Table 1. Characteristics of studies comparing intravitreal bevacizumab (IVB) with intravitreal triamcinolone acetonide (IVT) in the treatment of uveitic cystoid macular edema

Study	Study design	Population	No. of patients with IVB vs IVT	Mean±SD patient age (years)	IVB vs IVT dose (mg)	Follow-up (months)	Etiology	Degree of control of intraocular inflammation
Bae et al,[18] 2011	Retrospective non-randomized controlled	Korea	10 vs 11	54.8±16.6	1.25 vs 4.0	6	None had a systemic or ocular disease other than the one causing uveitis or non-infectious uveitis	Complete control of uveitis (no cells in the anterior chamber)
Lasave et al,[15] 2009	Retrospective non-randomized controlled	Multinational	16 vs 20	45.6±13.2	2.5 vs 4.0	6		
Rahimi et al,[17] 2012	Randomized	Iran	31 vs 29	23.2±11.7	1.25 vs 4.0	6		
Soheilian et al,[16] 2010	Randomized	Iran	15 vs 16	33.1±16.2	1.25 vs 2.0	9		

Table 2. Best corrected visual acuity (BCVA) at 1, 3, and 6 months after intravitreal bevacizumab (IVB) or intravitreal triamcinolone acetonide (IVT)

Study	IVB		IVT		Weight (%)	Mean difference
	Mean±SD BCVA	No. of patient	Mean±SD BCVA	No. of patients		IV, Random, 95% CI
At 1 month*						
Bae et al,[18] 2011	0.47±0.47	10	0.38±0.21	11	9.4	0.09 (-0.23, 0.41)
Lasave et al,[15] 2009	1.1±0.4	16	0.8±0.4	20	12.7	0.30 (0.04, 0.56)
Rahimi et al,[17] 2012	0.14±0.08	31	0.15±0.08	29	49.6	-0.01 (-0.05, 0.03)
Soheilian et al,[16] 2010	0.76±0.27	15	0.71±0.04	16	28.3	0.05 (-0.09, 0.19)
Total (95% CI)		**72**		**76**	**100.0**	**0.06 (-0.05, 0.16)**
At 3 months†						
Bae et al,[18] 2011	0.06±0.06	10	0.07±0.06	11	38.6	-0.01 (-0.06, 0.04)
Lasave et al,[15] 2009	1±0.3	16	0.7±0.6	20	13.8	0.30 (0.07, 0.53)
Rahimi et al,[17] 2012	0.52±0.45	31	0.41±0.21	29	17.1	0.11 (-0.07, 0.29)
Soheilian et al,[16] 2010	0.66±0.1	15	0.56±0.02	16	35.3	0.10 (0.05, 0.15)
Total (95% CI)		**72**		**76**	**100.0**	**0.09 (-0.01, 0.18)**
At 6 months‡						
Bae et al,[18] 2011	0.54±0.39	10	0.45±0.36	11	4.2	0.09 (-0.23, 0.41)
Lasave et al,[15] 2009	0.8±0.4	16	0.7±0.3	20	7.2	0.10 (-0.14, 0.34)
Rahimi et al,[17] 2012	0.03±0.04	31	0.03±0.04	29	46.2	0.00 (-0.02, 0.02)
Soheilian et al,[16] 2010	0.6±0.07	15	0.52±0.02	16	42.4	0.08 (0.04, 0.12)
Total (95% CI)		**72**		**76**	**100.0**	**0.04 (-0.02, 0.11)**

* *Heterogeneity: $Tau^2 = 0.01$, $Chi^2 = 6.03$, $df = 3$ ($p = 0.11$), $I^2 = 50\%$; test for overall effect: $Z = 1.02$ ($p = 0.31$)*
† *Heterogeneity: $Tau^2 = 0.01$, $Chi^2 = 13.85$, $df = 3$ ($p = 0.003$), $I^2 = 78\%$; test for overall effect: $Z = 1.77$ ($p = 0.08$)*
‡ *Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 14.60$, $df = 3$ ($p = 0.002$), $I^2 = 79\%$; test for overall effect: $Z = 1.28$ ($p = 0.20$)*

initial treatment; heterogeneity between studies was low with I^2 of 0%, 82%, and 86%, respectively. The two groups did not differ significantly in change in CMT at 1 month (WMD = 5.17, 95% CI = 9.20-19.53, p = 0.48) or 3 months (WMD = 43.3, 95% CI = -11.6-98.2, p = 0.12). At 6 months, change in CMT was higher in the IVT than IVB group (WMD = 40.6, 95% CI = 8.2-73.0, p = 0.01) [**Table 3**].

Publication bias

Based on funnel plots for the analysis of BCVA and CMT, no obvious evidence of publication bias was found for the treatment outcome estimates (BCVA and CMT at 3 months) [**Figure**]. Nonetheless, the number of enrolled studies was relatively low; Egger's method and Begg's method were additionally applied to measure any publication bias and found no significant publication bias (BCVA at 3 months: Egger method, p = 0.86; Begg method, p = 0.57; CMT at 3 months: Egger method, p = 0.26; Begg method, p = 0.12).

Discussion

In our meta-analysis, IVT and IVB did not differ significantly in improvement of BCVA or CMT up to 6 months after initial treatment, except that at 6 months IVT was more effective than IVB in reducing CMT. Nonetheless, triamcinolone can lead to a profound increase in intraocular pressure (IOP), particularly in younger patients. Patients with uveitic macular edema are usually <70 years old; their risk of a triamcinolone-induced ocular hypertension and secondary steroid-induced open-angle glaucoma may therefore be higher than for those with diabetic macular edema. In addition, the underlying uveitis can independently be associated with elevated IOP. Nonetheless, if uveitis results in ocular hypotony and uveitic macular edema, IVT may be used in this special clinical situation.

In the Lasave et al study,[15] IOP was medically controlled with topical anti-glaucoma medications in all 20 but one (5%) eye, which later required trabeculectomy, whereas another eye showed a marked progression of cataract in the IVT group. In the Bae et al study,[18] IOP increased within one day to 8 weeks of IVT application in 11 patients; IOP spontaneously decreased in five patients, and was medically controlled by topical anti-glaucomatous medications or by systemic acetazolamide in four. Anti-glaucomatous filtration surgery was required in one patient. As no change was detected in the optic disk appearance in any of the patients, the intravitreal steroid-induced IOP increase could have been secondary to ocular hypertension rather than open-angle glaucoma.[18] In the remaining two studies,[16,17] patients who developed a steroid-induced IOP rise were well controlled with topical anti-glaucoma medication; systemic therapy or filtration surgery was not required, and there was no change in the optic nerve head appearance.

Besides IVT, both intravitreal slow-release devices of dexamethasone (orzudex) and fluocinolone (Retisert) demonstrate an intraocular anti-inflammatory effect in patients with uveitis and result in decreased macular edema and increased visual acuity.[19-25] Nonetheless, neither has

Table 3. Central macular thickness (CMT) at 1, 3, and 6 months after intravitreal bevacizumab (IVB) or intravitreal triamcinolone acetonide (IVT)

Study	IVB		IVT		Weight (%)	Mean difference
	Mean±SD CMT	No. of patient	Mean±SD CMT	No. of patients		IV, Random, 95% CI
At 1 month*						
Bae et al,[18] 2011	220.6±239	10	227.1±95.1	11	0.8	-6.50 (-164.93, 151.93)
Lasave et al,[15] 2009	332.1±120.7	16	303.3±164	20	2.4	28.80 (-64.28, 121.88)
Rahimi et al,[17] 2012	254.54±30.15	31	251.75±30.41	29	87.8	2.79 (-12.54, 18.12)
Soheilian et al,[16] 2010	328.3±72.9	15	305.2±62.1	16	9.0	23.10 (-24.72, 70.92)
Total (95% CI)		**72**		**76**	**100.0**	**5.17 (-9.20, 19.53)**
At 3 months†						
Bae et al,[18] 2011	260.6±229.6	10	269.5±158.1	11	8.2	-8.90 (-179.13, 161.33)
Lasave et al,[15] 2009	323.4±108.1	16	289.4±141.2	20	20.9	34.00 (-47.46, 115.46)
Rahimi et al,[17] 2012	233.9±12.56	31	218.13±29	29	37.9	15.77 (4.33, 27.21)
Soheilian et al,[16] 2010	386.2±50.4	15	292.4±52.2	16	33.0	93.80 (57.68, 129.92)
Total (95% CI)		**72**		**76**	**100.0**	**43.33 (-11.56, 98.23)**
At 6 months‡						
Lasave et al,[15] 2009	344.7±135	16	296±134.4	20	10.5	48.70 (-39.87, 137.27)
Rahimi et al,[17] 2012	221.06±12.13	31	199.27±27.64	29	46.1	21.79 (10.86, 32.72)
Soheilian et al,[16] 2010	345±13.2	15	286.4±30	16	43.4	58.60 (42.45,74.75)
Total (95% CI)		**62**		**65**	**100.0**	**40.59 (8.16, 73.03)**

* *Heterogeneity: Tau² = 0.00, Chi² = 0.90, df = 3 (p = 0.83), I² = 0%; test for overall effect: Z = 0.70 (p = 0.48)*
† *Heterogeneity: Tau² = 2034.79, Chi² = 16.50, df = 3 (p = 0.0009), I² = 82%; test for overall effect: Z = 1.55 (p = 0.12)*
‡ *Heterogeneity: Tau² = 563.00, Chi² = 13.81, df = 2 (p = 0.001), I² = 86%; test for overall effect: Z = 2.45 (p = 0.01)*

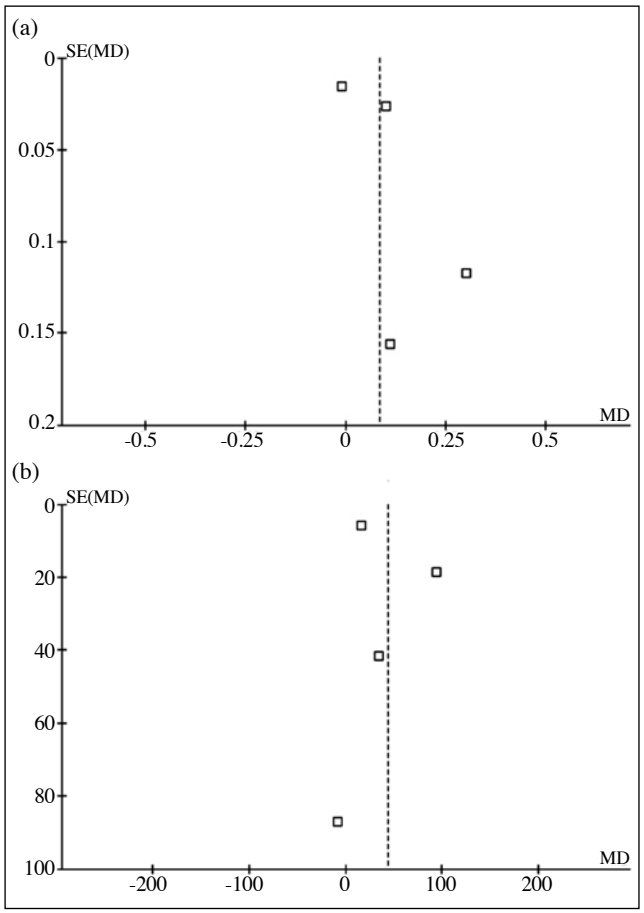

Figure. Funnel plots for publication bias: (a) best corrected visual acuity and (b) central macular thickness at 3 months after treatment.

been compared with intravitreally applied anti-VEGF drugs or IVT as treatment for uveitis.

There were limitations to our study. Only a few clinical studies were included in our meta-analysis, and each contained relatively few patients; the etiology of uveitis was heterogeneous. In addition, different studies used different optical coherence tomography devices; measurements could not be directly compared between studies. Despite this, funnel plots did not reveal any obvious evidence of a publication bias. Moreover, the follow-up duration was limited to 6 months; longer-term outcome was not known. The etiology of uveitis was usually not given or fully presented; results of our study can therefore refer only to the group of non-infectious uveitis. Information about the type of systemic treatment that might have been previously applied, and the degree of control of intraocular inflammation at the time of intraocular injection were not fully described. Periocular injection of steroids including subconjunctival application of steroids has been commonly used to treat edema in patients with uveitis who are non-responsive to topical steroids or non-steroidal anti-inflammatory drugs. Our study focused on comparison of intravitreal injection of drugs for uveitic macular edema; the method of peribulbar steroid injection was not evaluated.

Conclusion

IVT and IVB achieved comparable improvements in BCVA and reduction in CMT in patients with uveitic macular edema, although IVT was more effective than IVB in

reducing CMT at 6 months. This slight advantage of IVT may be outweighed by the disadvantage of a steroid-induced ocular hypertension with the risk of conversion to temporary secondary open-angle glaucoma. With respect to safety and visual improvement, IVB may be the first choice for treatment of uveitic macular edema.

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Declaration

Jost B. Jonas is a consultant for Allergan, Merck Sharp & Dohme, Alimera, Boehringer Ingelheim, and Sanofi, as well as patent holder with Biocompatible UK (treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and/or anti-angiogenic factor; patent number: 20120263794), and patent application with University of Heidelberg (agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; Europäische Patentanmeldung 15 000 771.4). All other authors have disclosed no conflicts of interest.

References

1. *Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80:332-6.*
2. *Okhravi N, Lightman S. Cystoid macular edema in uveitis. Ocul Immunol Inflamm. 2003;11:29-38.*
3. *Lardenoye CW, Rothova A, Van Kooij B. Impact of macular edema on visual acuity in uveitis. Ophthalmology. 2006;113:1446-9.*
4. *Rothova A. Inflammatory cystoid macular edema. Curr Opin Ophthalmol. 2007;18:487-92.*
5. *Cordero Coma M, Sobrin L, Onal S, Christen W, Foster CS. Intravitreal bevacizumab for treatment of uveitic macular edema. Ophthalmology. 2007;114:1574-9.*
6. *Baffi J, Fine HF, Reed GF, Csaky KG, Nussenblatt RB. Aqueous humor and plasma vascular endothelial growth factor in uveitis-associated cystoid macular edema. Am J Ophthalmol. 2001;132:794-6.*
7. *Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin. Experiment Ophthalmol. 2001;29:2-6.*
8. *Degenring RF, Jonas JB. Intravitreal injection of triamcinolone acetonide as treatment of chronic uveitis. Br J Ophthalmol. 2003;87:361.*
9. *Angunawela RI, Heatley CJ, Williamson TH, et al. Intravitreal triamcinalone acetonide for refractory uveitic cystoid macular oedema: longterm management and outcome. Acta Ophthalmol Scand. 2005;83:595-9.*
10. *Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitreal triamcinolone in uveitis. Ophthalmology. 2005;112:1916.e1-7.*
11. *Finger PT, Chin K. Anti-vascular endothelial growth factor bevacizumab (Avastin) for radiation retinopathy. Arch Ophthalmol. 2007;125:751-6.*
12. *Becker MD, Heinz C, Mackensen F, Heiligenhaus A. Intravitreal bevacizumab (Avastin) as a treatment for refractory macular edema in patients with uveitis: a pilot study. Retina. 2008;28:41-5.*
13. *Sallam A, Comer RM, Chang JH, et al. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. Arch Ophthalmol. 2008;126:200-5.*
14. *Weiss K, Steinbrugger I, Weger M, et al. Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab. Eye (Lond). 2009;23:1812-8.*
15. *Lasave AF, Zeballos DG, El-Haig WM, Díaz-Llopis M, Salom D, Arevalo JF. Short-term results of a single intravitreal bevacizumab (avastin) injection versus a single intravitreal triamcinoloneacetonide (kenacort) injection for the management of refractory noninfectious uveitic cystoid macular edema. Ocul Immunol Inflamm. 2009;17:423-30.*
16. *Soheilian M, Rabbanikhah Z, Ramezani A, Kiavash V, Yaseri M, Peyman GA. Intravitreal bevacizumab versus triamcinolone acetonide for refractory uveitic cystoid macular edema: a randomized pilot study. J Ocul Pharmacol Ther. 2010;26:199-206.*
17. *Rahimi M, Shahrzad SS, Banifatemi M, Rahimi M, Shahrzad SS. Comparison of intravitreal injection of bevacizumab and triamcinolone acetonide in the treatment of uveitic macular edema. Iran J Immunol. 2012;9:136-44.*
18. *Bae JH, Lee CS, Lee SC. Efficacy and safety of intravitreal bevacizumab compared with intravitreal and posterior sub-tenon triamcinoloneacetonide for treatment of uveitic cystoid macular edema. Retina. 2011;31:111-8.*
19. *Pleyer U, Klamann M, Laurent TJ, et al. Fast and successful management of intraocular inflammation with a single intravitreal dexamethasone implant. Ophthalmologica. 2014;*
20. *Tomkins-Netzer O, Taylor SR, Bar A, et al. Treatment with repeat dexamethasone implants results in long-term disease control in eyes with noninfectious uveitis. Ophthalmology 2014;121:1649-54.*
21. *Zarranz-Ventura J, Carreño E, Johnston RL, et al. Multicenter study of intravitreal dexamethasone implant in noninfectious uveitis: indications, outcomes, and reinjection frequency. Am J Ophthalmol. 2014;158:1136-45.*
22. *Taylor SR, Isa H, Joshi L, Lightman S. New developments in corticosteroid therapy for uveitis. Ophthalmologica. 2010;224(Suppl 1):46-53.*
23. *Patel CC, Mandava N, Oliver SC, Braverman R, Quiroz-Mercado H, Olson JL. Treatment of intractable posterior uveitis in pediatric patients with the fluocinolone acetonide intravitreal implant (Retisert). Retina. 2012;32:537-42.*
24. *Shen BY, Punjabi OS, Lowder CY, Sears JE, Singh RP. Early treatment response of fluocinolone (retisert) implantation in patients with uveitic macular edema: an optical coherence tomography study. Retina. 2013;33:873-7.*
25. *Arcinue CA, Cerón OM, Foster CS. A comparison between the fluocinolone acetonide (Retisert) and dexamethasone (Ozurdex) intravitreal implants in uveitis. J Ocul Pharmacol Ther. 2013;29:501-7.*

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TO DRIVE DOWN IOP WITH LESS DISCOMFORT *†

***Study Design:** A one-year, multicenter, randomized, double-masked, active-controlled, parallel-group trial of AZARGA® Suspension and dorzolamide/timolol in patients with open-angle glaucoma or ocular hypertension who required a change in therapy due to elevated IOP while receiving IOP-lowering medication. Patients (N=437) were dosed twice daily. The primary efficacy endpoint was a non-inferiority comparison of mean IOP at the 8 am, 10 am, and 4 pm time points at Month 6. AZARGA® Suspension provided clinically relevant IOP-lowering efficacy. Changes from baseline data were descriptive statistics.[1]

†**Study Design:** Prospective, double-masked, parallel-group, randomized clinical trial. Patients completed an ocular discomfort assessment (based on burning, stinging, a feeling of heat or warmth, sharp pain, or smarting pain) for their current intraocular pressure-lowering therapy at baseline and for the study medication after 1 week of treatment. The primary efficacy parameter was mean discomfort score assessed at study end (Week 1). AZARGA® Suspension demonstrated significantly less ocular discomfort than dorzolamide/timolol.[2]

IOP=Intraocular Pressure

AZARGA® Important note: Before prescribing, please consult full prescribing information. **Presentation:** 1 ml of suspension contains 10 mg brinzolamide and 5 mg timolol (as timolol maleate). **Indication:** Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. **Dosage:** The dose is one drop of AZARGA® eye drops, suspension in the conjunctival sac of the affected eye(s) twice daily. Nasolacrimal occlusion or gently closing the eyelid after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions. If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) twice daily. When substituting another ophthalmic antiglaucoma agent with AZARGA® eye drops, suspension, the other agent should be discontinued and AZARGA® eye drops, suspension should be started the following day. **Method of administration:** For ocular use. Instruct patients to shake the bottle well before use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use. **Contraindications:** • Hypersensitivity to the active substances, or to any of the excipients. • Bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease. • Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock. • Severe allergic rhinitis and bronchial hyperreactivity; hypersensitivity to other beta-blockers. • Hyperchloraemic acidosis • Severe renal impairment. • Hypersensitivity to sulphonamides **Precautions/Warnings:** Systemic effects Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of timolol maleate. Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile insulin-dependent diabetes as beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia. They may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension. AZARGA® eye drops, suspension contains brinzolamide, a sulphonamide. The same types of undesirable effects that are attributable to sulphonamides may occur with topical administration. There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZARGA® eye drops, suspension. The concomitant administration of AZARGA® eye drops, suspension and oral carbonic anhydrase inhibitors has not been studied and is not recommended. Anaphylactic reactions While taking beta-adrenergic blocking agents, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. Concomitant therapy Timolol may interact with other medicinal products. The effect on intraocular pressure or the known effects of systemic beta blockade may be potentiated when AZARGA® eye drops, suspension is given to patients already receiving an oral beta-adrenergic blocking agent. The use of two local betaadrenergic blocking agents or two local carbonic anhydrase inhibitors is not recommended. Ocular effects Caution should be utilised in treating patients with pseudoexfoliative glaucoma or pigmentary glaucoma, and recommend to closely monitor IOP. Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination in elderly patients. AZARGA® eye drops, suspension is absorbed systemically and therefore this may occur with topical administration. The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended. AZARGA® eye drops, suspension contains benzalkonium chloride as preservative, which has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy and requires close monitoring with frequent or prolonged use. It may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of AZARGA® and wait 15 minutes after instillation of the dose before reinsertion. **Adverse reactions:** Common: dysgeusia, blurred vision, eye pain, eye irritation, foreign body sensation in eyes Uncommon: insomnia, corneal erosion, punctate keratitis, dry eye, eye discharge, eye pruritus, ocular hyperaemia, blepharitis, allergic conjunctivitis, corneal disorder, anterior chamber flare, conjunctival hyperaemia, eyelid margin crusting, astenopia, abnormal sensation in eye, eyelids pruritus, allergic blepharitis, erythema of eyelid, decreased blood pressure, chronic obstructive pulmonary disease, pharyngolaryngeal pain, rhinorrhoea, cough, hair disorder, lichen planus **Interactions:** No interaction studies have been performed with AZARGA® eye drops, suspension. **Packs:** 5 ml **Legal classification:** PTSTS3

References:

1. Manni G, Denis P, Chew P, et al. The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/ timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. J Glaucoma. 2009;18(4):293-300.
2. Vold SD, Evans RM, Stewart RH, Walters T, Mallick S. A one-week comfort study of BID-dosed brinzolamide 1%/timolol 0.5% ophthalmic suspension fixed combination compared to BID-dosed dorzolamide 2%/timolol 0.5% ophthalmic solution in patients with open-angle glaucoma or ocular hypertension. J Ocul Pharmacol Ther. 2008;24(6):601-605.

NOVARTIS

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AZARGA®
(brinzolamide 10mg/ml+timolol 5mg/ml) eyedrops, suspension

Lower IOP with less discomfort.

LUCENTIS®: STATE-OF-THE-ART PREFILLED SYRINGE[1-3]

4 EASY STEPS[1]

1 RELEASE

Release the syringe from its pack

- Use aseptic technique throughout the procedure
- The prefilled syringe is for single use only
- Do not use if any part of the packaging is damaged or if the solution is discolored, cloudy, or contains particles

2 SNAP

Snap off the protective syringe cap

- Do not twist – the cap must be snapped off

3 ATTACH

Attach the injection needle of your choice

- Attach a 30G x 1/2 inch sterile injection needle
- Do not wipe the needle at any time

4 SET

Set the dose

Align the edge below the dome of the stopper with the **dose mark**

- The rubber stopper is non-retractable to prevent air from being drawn into the syringe
- 0.05 mL equals 0.5 mg of ranibizumab

EASY TO HANDLE to potentially minimize ocular risk[1,2]

- Non-retractable stopper[1]
- Advanced siliconization process[1,4]
- Easy to hold[*]

EASY TO USE with fewer preparation steps[1]

EASY TO SAVE TIME in your daily practice[3]

* versus the LUCENTIS® vial, 97% out of the 98 physicians surveyed (from 6 countries). The physicians had experience of ≥10 LUCENTIS® PFS injections

Easy to offer the benefits of LUCENTIS® to your nAMD, DME, BRVO, CRVO, and myopic CNV patients[1-3]

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LUCENTIS RANIBIZUMAB
DESIGNED TO SAVE SIGHT

Broad spectrum potent antibacterials

Cravit® ophthalmic solution

Levofloxacin 0.5%

- Efficacy & Safety [1,2]
- High Ocular Penetration [3]
- Preservative Free

[Composition]

Cravit ophthalmic solution is a pale to light yellow, clear sterile aqueous solution. Each mL contains 5 mg of levofloxacin. Its pH is 6.2-6.8 and its osmotic pressure ratio is 1.0-1.1.

[Indications]

<Indicated bacteria>

Susceptible strains of Staphylococcus sp., Streptococcus sp., Streptococcus pneumoniae, Enterococcus sp., Micrococcus sp., Moraxella sp., Corynebacterium sp., Klebsiella sp., Enterobacter sp., Serratia sp., Proteus sp., Morganella morganii, Haemophilus influenza, Haemophilus aegyptius [Koch-Weeks bacillus], Pseudomonas sp., Pseudomonas aeruginosa, Stenotrophomonas (Xanthomonas) maltophilia, Acinetobacter sp., and Propionibacterium acnes.

<Indications>

Blepharitis, dacryocystitis, hordeolum, conjunctivitis, tarsadenitis, keratitis (including corneal ulcer), and aseptic treatment during a perioperative period for ocular surgery.

[Dosage and Administration]

Usually, instill 1 drop a time 3 times daily. The dosage may be adjusted according to the patient's symptoms.

[Contraindications]

(Cravit opthtalmic solution is contraindicated in the following patients.)

Patients with a history of hypersensitivity to the ingredient of this product, ofloxacin or any quinolone antibiotics.

[Precautions]

1. In order to avoid the emergence of resistant bacteria, bacterial susceptibility should be confirmed and treatment with this drug should be limited to the minimum period required for the eradication of the infection.
2. The efficacy of this product to methicillin-resistant Staphylococcus aureus (MRSA) has not been proved. Therefore, other drug having a potent anti-MRSA activity should be administered immediately to patients positively infected with MRSA and not showing any improvement of symptoms with this product.

(Full prescribing information shall be available upon request)

Reference:

1. Masahiko Usui. Clinical Evaluation of Levofloxacin Ophthalmic Solution – A Multicenter Phase III Double-masked Clinical Trial. J. Eye. 1997, 14(4): 641-648.
2. Masahiko Usui. Clinical Evaluation of Levofloxacin Ophthalmic Solution – A Multicenter Phase III Open Label Trial. J. Eye. 1997, 14(7): 1113-1118
3. Fukuda M. et al. General purpose antimicrobial ophthalmic solutions evaluated using new pharmacokinetic parameter of maximum drug concentration in aqueous. Jpn J Ophthalmol. 2002 Jul-Aug;46(4):384-90.

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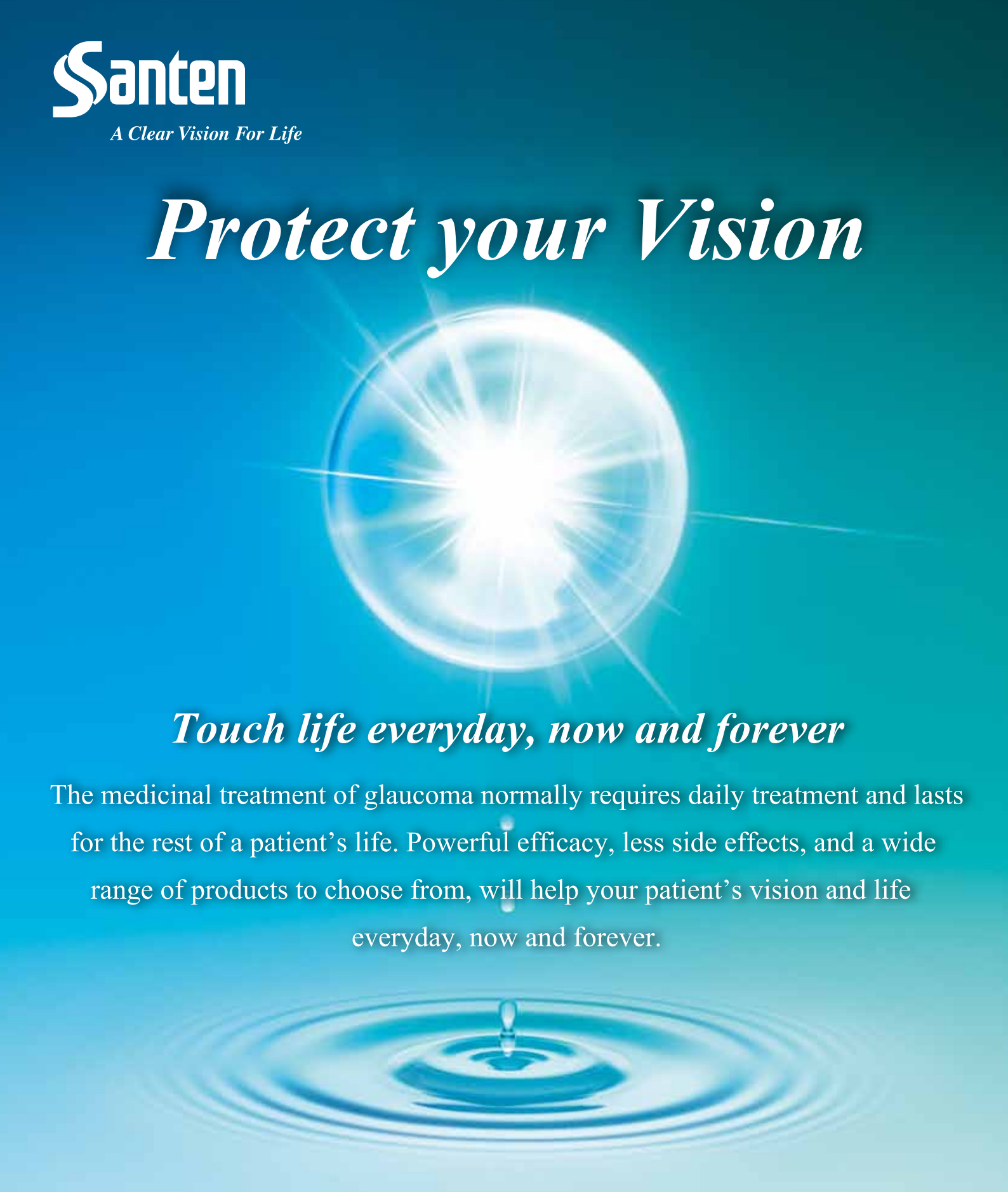
For Healthcare Professionals Only

Santen

A Clear Vision For Life

Protect your Vision



Touch life everyday, now and forever

The medicinal treatment of glaucoma normally requires daily treatment and lasts for the rest of a patient's life. Powerful efficacy, less side effects, and a wide range of products to choose from, will help your patient's vision and life everyday, now and forever.

Cosopt
dorzolamide HCl 2% -timolol maleate 0.5% eye drops

TRUSOPT®
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TIMOPTOL®
timolol maleate 0.5% eye drops

TAFLOTAN
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NEW! AcrySof® IQ PanOptix™ Presbyopia-Correcting IOL

Designed for more natural adaptability

Featuring ENLIGHTEN™ (**EN**hanced **LIGHT EN**ergy) Optical Technology to mimic the performance of a healthy crystalline lens, the AcrySof® IQ PanOptix™ IOL is the natural choice for advanced presbyopia correction:

- **Exceptionally high light utilization in a presbyopia-correcting IOL.** Transmits 88% of light to help provide crisp quality of vision at all distances.[1]
- **More comfortable near to intermediate range of vision.** Provides a more natural intermediate focal point of 60 cm, which is preferred for real-life tasks, such as computer work, over the 80 cm distance offered by other trifocals.[2-4]
- **Less dependence on pupil size.** 4.5 mm diffractive zone designed for excellent performance in all lighting conditions.[2]

To learn more about the AcrySof® IQ PanOptix™ Presbyopia-Correcting IOL, talk to your Alcon sales representative.

1. AcrySof® IQ PanOptix™ IOL Directions for Use. 2. PanOptix™ Diffractive Optical Design. Alcon internal technical report: TDOC-0018723. Effective date 19 Dec 2014. 3. Charness N, Dijkstra K, Jastrzembski T, et al. Monitor viewing distance for younger and older workers. Proceedings of the Human Factors and Ergonomics Society 52nd Annual Meeting, 2008. http://www.academia.edu/477435/Monitor_Viewing_Distance_for_Younger_and_Older_Workers. Accessed April 9, 2015. 4. Average of American OSHA, Canadian OSHA and American Optometric Association Recommendations for Computer Monitor Distances.

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