JOURNAL CLUB: TREATMENT OF RETINAL DISORDERS

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LEARNING OBJECTIVES

1. Understand the latest results from randomized clinical trials for the treatment of macular edema due to central retinal vein occlusion.
2. Identify the potential risks and benefits of the different effective therapies of anti-vascular endothelial growth factor (anti-VEGF) agents, steroids, and steroidal implants for reducing macular edema in central retinal vein occlusion.
3. Describe the most recent data from two large clinical trials comparing ranibizumab and bevacizumab in the treatment of wet macular degeneration.

CME QUESTIONS

1. Which of the following therapeutic modalities for the treatment of macular edema due to central retinal vein occlusion were NOT studied in a large randomized clinical trial?
   a. Intravitreal preservative-free triamcinolone acetonide
   b. Intravitreal ranibizumab
   c. Intravitreal bevacizumab
   d. Dexamethasone intravitreal implant
   e. All of the above

2. True/False: While intravitreal steroidal injections and steroid implants pose known risks for ocular hypertension and glaucoma, these risks, to a much lesser degree, have also been reported following frequent intravitreal anti-VEGF treatments.

3. True/False: In the treatment of neovascular age-related macular degeneration, ranibizumab and bevacizumab, administered monthly or as needed, had similar visual outcomes over a 2-year period.

KEYWORDS

1. Central Retinal Vein Occlusion
2. Macular Edema
3. Intravitreal Injection
4. Anti-Vascular Endothelial Growth Factor (Anti-VEGF)
5. Dexamethasone Intravitreal Implant

INTRODUCTION

Approximately 0.1% to 0.5% of patients of middle age and older will suffer from a central retinal vein occlusion.1,2,3 Vision loss can be devastating rendering patients to be legally blind in the affected eye. The Central Vein Occlusion Study published in 1997 showed that patients presenting with less than 20/200 vision only had a 20% chance of improving their vision.4 Approximately 31% of patients with less than 20/200 vision developed iris and angle neovascularization. Loss of vision can be due to non-perfusion/retinal ischemia with resultant macular edema. Clinical trials in the management of central retinal vein occlusions over the last three years have revolutionized how retina specialists treat macular edema. Goals are to reduce capillary permeability and inhibit expression of VEGF genes and their metabolic pathways.5 As a result, multiple options exist now as part of the armamentarium. Unfortunately, many of these new treatments (intravitreal triamcinolone acetonide, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, sustained release dexamethasone intravitreal implant) require repeated treatments. Patients have benefited from the newer modalities by improving chances of gaining functional vision after experiencing a devastating visually compromising disease.

CLINICAL TRIALS USING CORTICOSTEROIDS

1) SCORE-INTRAVITREAL PRESERVATIVE-FREE TRIAMCINOLONE ACETONIDE
A Randomized Trial Comparing the Efficacy and Safety of Intravitreal Triamcinolone With Observation to Treat Vision Loss Associated With Macular Edema Secondary to Central Retinal Vein Occlusion

The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 5

The SCORE Study Research Group 6

The SCORE study compared the efficacy preservative-free intravitreal triamcinolone to observation. Two-hundred and seventy-one patients participated in this multicenter, randomized, clinical trial. The primary outcome measure was improvement in visual acuity of 15 letters or more from baseline to 12 months. The study looked at 1mg and 4mg dosages of a specially formulated, preservative-free triamcinolone. Patients could be retreated at every 4 months if deemed necessary by
the time of first dexamethasone implant treatment was significantly associated with a lower likelihood of achieving an improvement of 15 letters or more or a reduction of 200 μm or more of central retinal thickness. This suggests sooner treatment would be better for these patients.

**CLINICAL TRIALS USING ANTI-VEGF AGENTS**

1) CRUISE-RANIBIZUMAB

Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study.


The CRUISE study assessed monthly injections of 0.3 mg vs. 0.5 mg ranibizumab in a prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trial which included 392 participants with macular edema due to CRVO. Patients were randomized. Primary outcome was to measure at 6 months, the mean change of best corrected vision. In the ranibizumab groups, 46.2% (0.3mg) and 47.7% (0.5mg) of patients gained 15 letters or more at month 6 as compared to the sham group which only 16.9% gained 15 letters or more at month 6. At 12 months, similar results were seen with 47.0% (0.3mg) and 50.8% (0.5mg) and sham group, 33.1%. In the extension study for CRUISE, called HORIZON, reduced follow up and fewer ranibizumab injections were noted during the second year of follow up and more frequent follow up than every 3 months may be required. Further study has shown that patient-reported visual function through 6 months noted improvement using the 25-item National Eye Institute Visual Function Questionnaire.

2) COPERNICUS-AFLIBERCEPT

COPERNICUS (Controlled Phase 3 Evaluation of Repeated intravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety)

The COPERNICUS study assessed aflibercept-an endothelial growth factor-trap in macular edema secondary to CRVO. This multicenter, randomized, prospective, controlled trial had a total of 189 eyes that were randomized to either sham or 2mg of aflibercept monthly for 6 months. 15-letter gain or more in best-corrected visual acuity at 6 months were noted in 56.1% of aflibercept treated eyes as compared to 12.3% sham eyes. A total of 17.3 letters gained versus a loss of 4.0 letters in sham-treated eyes. Progression to any neovascularization occurred in 6.8% of eyes treated with sham compared to zero of aflibercept treated eyes. As a result, monthly intravitreal injections of aflibercept in eyes with macular edema from CRVO are recommended in improving visual acuity and stopping progression to neovascularization.
RANIBIZUMAB AND BEVACIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

1) CATT-U.S.A.  
2) IVAN-EUROPE

Wet macular degeneration affects approximately 10% of the 10 million patients a year who develop macular degeneration. Two recent studies compared the efficacy and safety of ranibizumab to a bevacizumab in the treatment of wet macular degeneration. CATT was a multicenter, single-blind, noninferiority trial, where 1208 patients with neovascular AMD received intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. At 2 years, the CATT showed that ranibizumab and bevacizumab were similar in visual acuity benefits. Treatment as needed resulted in less gain in visual acuity, whether instituted at enrollment or after 1 year of monthly treatment. There were no differences between drugs in rates of death or arteriothrombotic events. IVAN, the European equivalent study, at 1 year, showed that best corrected visual acuity with monthly and as needed treatment were equivalent. The two drugs’ treatment regimens having similar efficacy and safety.

CME ANSWERS

1. C
2. True
3. True

REFERENCES

LEARNING OBJECTIVES

The attendee will be able to:

1. Discuss the results of selenium in the treatment of Graves’ orbitopathy
2. Outline the effects of bilateral subtotal thyroidectomy compared to total thyroidectomy on the progression of Graves’ orbitopathy
3. Learn about the long-term outcome of Graves’ orbitopathy in patients undergoing total thyroidectomy compared to total thyroid ablation
4. Review the data on the risk of developing or worsening of Graves’ orbitopathy after radioiodine therapy
5. Better understand the possible role of protracted hypofractionated radiotherapy in the treatment of Graves’ orbitopathy

KEYWORDS

1. Selenium
2. Graves’ Orbitopathy
3. Thyroidectomy
4. Radioiodine
5. Radiotherapy

INTRODUCTION

Graves’ orbitopathy (GO) is the most common cause of unilateral and bilateral proptosis in clinical practice. GO is most often associated with hyperthyroidism due to Graves’ disease (GD) but some patients can be euthyroid or hypothyroid.\(^1\)\(^2\) Approximately 70% of patients with GD have subclinical evidence of GO, but fortunately few patients (less than 5%) have severe disease resulting in visual loss from a compressive optic neuropathy. The majority of patients with GO have mild symptomatic disease that requires only supportive therapy. Although great strides have been made in our understanding, detection and management of GO there still remains several unanswered questions. In particular two important questions that still remain are: 1) Which patient with GD will develop GO or have worsening of their GO? 2) What is the optimum treatment regimen for patients with GO? This symposium will review 4 recently published clinical trials on the effect of GD treatment (medical, surgical, and radioactive iodine) on the development and progression of GO. In addition, the results of a pilot study on the use of prolonged low dose orbital radiation in GO will be discussed.

SELENIUM AND GRAVE’S ORBITOPATHY

Selenium is a non-metallic chemical element. Commercially it is used in the production of glass, pigments and DC surge protectors. More importantly selenium, through the effects of selenoproteins, has been found to play an important role in cell development and proliferation, oxidative stress protection and production of T\(_3\). Of all the organs in the human body, the thyroid gland contains the largest amount of selenium. It plays an important part in the proper functioning of the thyroid and in some cases the pathogenesis of thyroid disease. The human ingestion of selenium derives mainly from plants and animals feeding off of soil containing selenium.\(^3\)
The European Group on Graves’ Orbitopathy (EUGOGO, www.eugogo.eu) is a multidisciplinary consortium of endocrinologists, ophthalmologists, basic scientists and neuroradiologists who have a special clinical and research interest in Graves’ orbitopathy (GO). Comprised of 6 European academic institutions from 5 countries (Holland, Germany, Switzerland, Italy and Greece), the EUGOGO conducted a randomized, double-blind, placebo-controlled trial to determine the effect of selenium and pentoxifylline (compared to placebo) in patients with mild GO. The rationale for the use of selenium in GO was based on its anti-oxidant properties and for pentoxifylline based on its anti-inflammatory effects.

Over a 5 year period, 159 patients with mild GO were randomized into 3 groups: oral selenium (sodium selenite 100µ g BID), oral pentoxifylline (600 mg BID) and oral placebo (BID). An intention to treat analysis was carried through for all patients seen at the 3 month visit. Seven patients did not participate in the study beyond 1 month and therefore were not included in the final analysis. There were 54 patients in the selenium group, 48 in the pentoxifylline group and 50 in the placebo group. Ninety percent (137/152) patients completed the 12 month study.

Inclusion criteria were:

1. Presence of at least one sign of mild GO [soft tissue swelling NO SPECS class 2a and 2b (e.g., chemosis, mild to moderate eye lid swelling, exophthalmos ≤ 22 mm)]
2. GO disease duration < 18 months
3. No previous specific therapy for GO, except for local measures
4. Euthyroidism as a result of remission after a course of antithyroid drug (ATD) therapy, or euthyroidism for at least 2 months since commencing ATD or after thyroidectomy, or euthyroidism for at least 6 months after radioiodine therapy
5. Hypothyroid patients after thyroidectomy or radioiodine were replaced with levothyroxine
6. Age 18–70 years

Exclusion criteria were:

1. Soft tissue swelling NO SPECS class 2c (e.g. severe chemosis, severe eye lid swelling)
2. Exophthalmos >22 mm
3. Diplopia in primary or reading position, and/or ocular torticollis
4. Monocular duction in any direction < 20 degrees
5. Signs or symptoms of dysthyroid optic neuropathy
6. Pregnancy, drug and/or alcohol abuse, severe concomitant illness, inability to comply with the study protocol, no informed consent, or current use of selenium- or pentoxifylline-containing preparations

Patients were seen at baseline, 3 months, 6 months and 12 months. A single ophthalmologist, who was blinded to the treatment regimen, examined all patients at each study site. Patients received therapy for 6 months and then were followed for an additional 6 months (without therapy) to determine the presence of or a lack of a persistent effect from treatment. There were 2 primary outcome measures: change in eye assessment (a composite score consisting of: eyelid aperture, soft tissue involvement, exophthalmos, ocular motility and visual acuity) and the Graves’ orbitopathy-specific quality-of-life questionnaire (GO-QOL). Ocular improvement was defined as the occurrence of at least one of the following measures in one eye, without worsening of any of these measures in either eye: reduction of eyelid aperture by at least 2 mm, reduction in any of the Class 2 signs by at least one grade in the NOSPECS classification, reduction in exophthalmos by at least 2 mm, and increase in ocular motility by at least 8 degrees in any duction. Ocular deterioration was defined by any of the following: worsening by at least one grade in any of the NOSPECS class, appearance of a new NOSPECS class, decrease in visual acuity due to optic nerve involvement by at least one line on the Snellen chart, or other evidence (i.e., impaired color vision) or suspicion of optic nerve compression. The clinical activity score (CAS) and Gorman diplopia score was also recorded for each patient.

The average age of the patients was 43.0 years ± 11.0 in the selenium group, 44.6 years ±10.7 in the pentoxifylline group and 43.7 years ±12.4 in the placebo. The majority of patients were female (83%) and Caucasian (98%). The average duration of eye symptoms prior to entering the study ranged from 6 to 7.7 months for the 3 groups. The median baseline CAS was 3.5 for the selenium group, 3.0 for the pentoxifylline group and 3.0 for the placebo group. Soft tissue involvement was mild in 59% in the selenium group, 54% in the pentoxifylline group and 65% in the placebo group. Diplopia was absent in 80% of selenium group, 90% of the pentoxifylline group and 88% of the placebo group.

At 6 months the overall ophthalmic outcome was better in the selenium group compared to the placebo group (p=0.01) but there was no statistical difference in the ophthalmic outcome of the pentoxifylline group compared to placebo group (p=0.12). GO improved in 61% in the selenium group, 35% in the pentoxifylline group and 36% in the placebo group. GO worsened in 7% in the selenium group, 10% in the pentoxifylline group and 26% in the placebo group (selenium compared to placebo, p=0.01). The improvement in GO was mainly driven by improvement in eyelid aperture and soft tissue involvement. At 6 months GO-QOL scores were significantly better in the selenium group compared to the placebo group (p<0.001). In comparison, the GO-QOL scores were not statistically significant for the pentoxifylline group compared to the placebo group (p=0.57). At 6 months the only statistically significant outcome observed in the pentoxifylline group compared to the placebo group was improvement in soft tissue signs (p=0.02) but that improvement was not sustained at the 12 month follow-up visit. Fewer patients in the selenium group experienced a worsening of their symptoms compared to the placebo (p=0.02) and the pentoxifylline group (p=0.05).
GO compared to patients in the placebo group (17% vs 43% respectively, p=0.004). At 12 months the beneficial response to selenium both clinically and based on the GO-QOL questionnaire was maintained.

There was no adverse drug reaction in any patients taking selenium. Potential concerns of selenium supplementation include diabetes mellitus and glaucoma. Seven patients taking pentoxifylline experienced an adverse event with 4 patients exiting the study within the first month of enrollment.

Based on this study selenium was found to reduce ocular involvement and slow the progression of disease in patients with mild GO. The authors cited two major limitations to their study. First, serum selenium concentrations were not measured during the study and second, the baseline serum selenium concentration status of the patients was not known to determine if the patients were deficient or not.

GRAVES’ DISEASE: SUBTOTAL THYROIDECTOMY VS TOTAL THYROIDECTOMY

There is a suggestion in the literature—although controversial and contradictory—that thyroidectomy can result in the development or progression of Graves’ orbitopathy (GO). This study was conducted to see if the type of surgery performed can have an effect on the development or worsening of GO. One hundred and ninety one out of 200 patients with GO completed five year follow-up after being randomized to either undergo total thyroidectomy (TT, n=96) or bilateral subtotal thyroidectomy (BST, n=95). No patient was below the age of 18 years and no patient had Graves’ disease for more than 2 years. Pre-operatively all patients were medically treated to be in a euthyroid state. Both patients and the examining ophthalmologist were blinded to the treatment received. A baseline eye examination was performed 1–2 weeks prior to surgery. All patients were determined to have mild Graves’ ophthalmology (GO) with a total eye score (TES) ≤ 4 based on the NO SPECS classification.

Clinical activity of GO was measured based on the clinical activity score (CAS). GO was considered active if the CAS was ≥3. The primary outcome of the study was change in GO and prevalence of recurrent hyperthyroidism. Following the baseline eye examination every patient was re-examined at 1, 3, 6, 9 and 12 months. After the first year annual examinations were performed for the next 4 years. During the pre-determined follow-up eye examinations, no change in GO was defined as a change in TES and/or CAS of < 2 points, disease progression was defined as an increase of ≥ 2 points in the TES and/or CAS, and disease improvement was defined as a decrease of ≥ 2 points in the TES and/or CAS.

All patients underwent a standardized surgical procedure. Two grams of thyroid tissue on each side of the gland was not removed during BST. Intraoperative nerve monitoring was not used during the dissection and identification of the recurrent laryngeal nerve (RLN). Serum concentrations of thyroid-stimulating hormone (TSH), free T3, free T4 and thyrotropin-binding inhibitory immunoglobulin (TBII) were measured at each visit.

At baseline the average TES was 3.64 in the BST group and 3.63 in the TT group. The CAS at baseline was 3.74 in the BST group and 3.69 in the TT group. There was no statistical difference in either of these scores between the 2 groups. At the 5 year follow-up 81% of patients in the BST group and 85% in the TT group had improvement in their GO (p=0.501). Five percent of patients in the BST group and 4% of patients in the TT group had no change in their eye disease (p=0.720). Nine percent of patients in BST group and 7% of patients in the TT group demonstrated progression of GO (p=0.586). Univariate analysis found a positive correlation between progression of GO with a body mass index ≥ 30 kg/m², ≥1 year interval between diagnosis of Graves’ disease and surgery and positive TBII level at 12 months. However, a multivariate analysis found that the TBII level was the only predictive risk factor for the progression of GO (p=0.007).

Nine patients developed hyperthyroidism following BST compared to no patients who underwent TT (p=0.002). Temporary RLN paresis was noted in 6 BST patients and 9 TT patients. Permanent RLN paresis was seen in 2 patients after BST and one patient after TT (p=0.556).

The study found no difference in the risk of progression of GO in patients undergoing BST compared to TT. However, those patients who underwent TT were less likely to develop recurrent hyperthyroidism.

GRAVES’ ORBITOPATHY: TOTAL THYROID ABLATION OR TOTAL THYROIDECTOMY

From 1998 to 2004 a total of 60 patients with mild or moderate Graves’ orbitopathy (GO) were randomized into a prospective and single-blinded study. In 2007 the 9 month results of this long-term cohort of patients was published. The study was originally designed to have 3 arms:

1) Total thyroidectomy (TX)
2) Total thyroid ablation (TTA), which consisted of near-total thyroidectomy plus radioactive iodine
3) Methimazole

Due to a discrepancy in the baseline characteristics, 30 patients from the methimazole group were excluded from the study. In addition 3 patients each from the TX and TTA group exited the study prior to the 3 month evaluation and 2 additional patients were lost to follow-up between the 3 month and 9 month follow-up examinations. Therefore at the 9 month follow-up time period there were a total of 25 patients analyzed in the TX group and 27 in the TTA group. As part of the study protocol all patients received 12 infusions of intravenous methylprednisolone (IVMP) over 10 weeks with the first 4 infusions dosed at 15/mg/kg/infusion and the remaining 8 infusions dosed at 7.5 mg/kg/infusion. Inclusion criteria were:
1. Recent-onset hyperthyroidism (≤6 months) treated only with antithyroid drugs
2. Thyroid volume 15 ml or greater, as assessed by ultrasound examination
3. Recent-onset GO (≤6 months), untreated, with the exception of local measures (artificial tears).
4. GO inclusion criteria comprised at least two of the following:
   a. Clinical activity score (CAS) of at least 3 out of 7
   b. Proptosis >21 mm in at least one eye;
   c. Intermittent or inconstant diplopia
   d. Eyelid width >9 mm in at least one eye

Exclusion criteria were:
1. Hyperthyroidism duration of 6 months or longer, or previous treatment with radioactive iodine or thyroidectomy
2. GO duration of 6 months or longer, or treated with steroids, orbital radiotherapy, or orbital decompression
3. Major contraindications to steroid treatment
4. Severe GO (defined by optic neuropathy or constant diplopia)

Prior to enrolling in the study all patients were in a constant euthyroid state for at least 10 weeks. The baseline characteristics of the TX and TTA group were similar. Thirty patients were randomized into each group. The mean age was 37 years in the TX group and 39 years in the TTA group. Twenty-one women were in the TX group and 20 women in the TTA group. The mean CAS was 3.0 in the TX group and 2.9 in the TTA group. The mean exophthalmometer measurement reading was 23 mm in the TX group and 23.2 in the TTA group. Diplopia was absent in 70% of the TX group and 60% of the TTA group. All patients underwent a baseline eye examination, followed by every 6 weeks during the IVMP therapy and then 3 and 6 months after the start of IVMP. The eye examination was performed by the same ophthalmologist who was not aware of the patients’ treatment. The primary outcome was the overall outcome of GO at 9 months after the IMVP. GO was considered improved if the patient met at least two of the following criteria:
1. Reduction in proptosis of at least 2 mm in at least one eye and with no increase of ≥2 mm in the contralateral eye
2. Reduction of CAS by at least 2 points
3. Reduction in eyelid width ≥2 mm in at least one eye, with no increase of ≥2 mm in the contralateral eye
4. Disappearance or improvement of diplopia (change of degree from constant to inconstant, from inconstant to intermittent, or from intermittent to absent).

GO was considered worsened if the patient had at least two of the following criteria:
1. Increase in proptosis by ≥2 mm in at least one eye
2. Increase of CAS by at least 2 points
3. Increase in eyelid width of ≥2 mm in at least one eye
4. New appearance or progression of diplopia (change of degree from intermittent to inconstant and from inconstant to constant).

At 9 months improvement in GO was more frequent in the TTA group than the TX group (p=0.0014). In addition more patients had stable GO and fewer patients had worsening GO in the TTA group compared to the TX group. Analysis of individual eye findings found that proptosis (p = 0.0271 and eyelid aperture (p = 0.0201) were statistically significantly in favor of the TTA group. Compared to >1% radioactive iodine uptake, the group of patients with < 1% radioactive iodine uptake (RAIU) at 9 months had a more favorable GO outcome (p = 0.0214). Four of 18 (22.2%) patients in the TX group had a RAIU <1.0% compared with 14 of 18 (77.7%) in the TTA group (p = 0.002).

The authors pointed out several very important limitations to their study. First, there was no medical arm for a direct comparison to surgery. Second, the study only included patients with mild GO which may have blunted the response to the IVMP and the relatively mild improvement seen in the cohort in general. Third, because all patients received IVMP it is not known what if any effect there would be if IVMP was not used. Fourth, and the reason for the follow-up paper, is the relatively short-term (9 month) outcome period.

Fifty two of the 60 patients were able to be analyzed with a mean follow-up of 88 ± 17.7 months. The outcome of GO (improvement, worsening or stability) was not different between the TX and TTA groups. Additional therapies given to patients such as orbital radiation, orbital decompression, strabismus surgery or eyelid surgery was also no different between the two groups with 7 patients in each group receiving some additional surgery. The median time needed to achieve the best possible GO outcome was longer in the TX group than the TTA group (24 months vs 3 months, p=0.0436). The median time for GO to improve was longer in the TX group than the TTA group (60 months vs 3 months, p=0.0344). A quality of life questionnaire found no difference between the groups with both groups having a large percentage of high scores.

**GRAVES’ HYPERTHYROIDISM: ANTI-THYROID DRUGS, SURGERY OR RADIOIODINE**

This 4 year follow-up study is based upon a prospective, randomized clinical trial published in 1992. From 1983 to 1990, 179 patients with Graves’ disease were enrolled with 168 patients analyzed during the original 24 month study period. Patients were stratified into 2 groups based on age: young (20–34 years of age) and old (35–55 years of age). In the younger group the patients were randomized to either receive medical therapy (methimazole) or surgical therapy (bilateral subtotal thyroidectomy). In the older group the patients were randomized into three subgroups: medical, surgical and iodine-131. The purpose of the study was to explore the effect of different treatment modalities for Graves’ disease on the development or exacerbation of Graves’ orbitopathy (GO) and to determine risk factors predictive of the development or exacerbation of GO.
GO was scored based on the modification of the American Thyroid Associations classification of ocular changes in Graves’ disease (ophthalmology-index score). The scoring system was based on 4 clinical manifestations: soft-tissue involvement, exophthalmos, ocular motility and visual loss. Each of these 4 categories was given a score of 1, 2 or 3 based on the severity. The total maximum score was 12 and a score of $\geq 1$ was considered indicative of the presence of GO. All patients were examined by a single ophthalmologist. A baseline eye examination was performed prior to any intervention and 1 year later if their score was 0. Patients with a score of $\geq 1$ were examined monthly until their examination improved or stabilized. The ophthalmologist was blinded to medical or iodine-131 therapy but was aware if the patient had undergone surgery. At baseline 22/168 (22%) patients had GO. Only four patients in the younger group had an ophthalmology-index score of 1. Eighteen patients in the older group had an ophthalmology-index score of $\geq 1$. Of these 18 patients, three had a score of 2 and one had a score of 4.

New GO developed in 22 (13%) patients and 8 (5%) had worsening of GO. Twenty-four of the patients had new or worsening of GO within the first year of treatment. There was no difference in the development or worsening of GO in the medical compared to the surgical subgroup of the younger group of patients. However, in the older group of patients, more patients (33%) in the iodine-131 subgroup developed or had worsening GO compared to the medical (10%) and surgical subgroups (16%). The relative risk of GO developing or worsening with iodine-131 was 3.2.

The increase in the ophthalmology-index score was small for the majority of patients. The mean increase of the ophthalmology-index score in the younger group was 1.5 for the medical subgroup and 2.3 for the surgical subgroup. For the older group the mean increase in the ophthalmology-index score was 3.0 in the medical subgroup, 1.8 in the surgical subgroup and 2.8 in the iodine-131 subgroup. Six patients in the older group required treatment for their GO with either corticosteroids or orbital radiation. No patient developed visual loss during the study.

Aside from treatment with iodine-131, the other positive predictive factors that correlated with worsening or development of GO were a pre-treatment serum concentration of T3 $\geq 5$ nmol/liter and the presence of lymphocytes in the thyroid. For those patients treated with iodine-131 with a serum concentration of T3 $\geq 5$ nmol/liter, the risk of GO was 58% compared to a 10% risk in those patients treated with iodine-131 with a T3 <5 nmol/liter.

An intention to treat analysis was performed on 179 patients that were originally randomized into the 2 groups and followed for a minimum of 48 months and maximum of 121 months. A questionnaire was given to every patient to assess their opinions on their disease course and treatment. Ninety-five percent of the patients in the medical subgroup, 98% in the surgical subgroup and 95% in the iodine-131 subgroup were satisfied with their treatment. The risk of relapse in terms of Graves’ disease was highest in the medially treated group (42% younger group vs 34% older group), followed by the iodine-131 group (21%) and then the surgically treated group (3% younger group vs 8% older group). The development or worsening of GO was not associated with disease relapse. Only one additional patient from the original study (iodine-131 group) developed GO 42 months after treatment. There was no correlation found between the development or worsening of GO in those patients treated with iodine-131 and hypothyroidism.

**GRAVES’ OPHTHALMOLOGY: PROTRACTED HYPOFRACTIONATED RADIOTHERAPY**

Currently there are no definitive treatment recommendations regarding the fractionation, duration and dosing of radiotherapy in patients with Graves’ orbitopathy (GO). In this pilot study, performed in Quebec, Canada, the authors evaluated the clinical and radiological effect of extended, low dose radiotherapy for GO. Specifically, a low dose of radiation (1Gy/week) was delivered over a 10 week period of time for a total dose delivered to each orbit of 10 Gy.

Only patients (18) with bilateral orbital involvement (36) were enrolled. Patients were followed prospectively for a minimum of 6 months. However, the median follow-up time was 18 months (range, 6–24 months). Analysis was performed on 2 groups of patients. Group I was composed of 9 patients who received only radiotherapy. Group II was composed of 9 patients who were treated with oral corticosteroids by their referring ophthalmologist or endocrinologist 2 months prior to radiation therapy. The median age of the cohort was 49 years with a range of 21–71 years. Sixteen patients were females and only one patient was euthyroid. A physical examination and magnetic resonance imaging (MRI) study was done before and 6 months after radiotherapy. Patients were also examined to determine ocular pain, palpebral edema, ocular itching, ocular motility, diplopia, conjunctival hyperemia, photophobia, visual acuity, ocular grittiness and tearing. GO activity was assessed based on the modified Mourits clinical activity score (CAS).

All patients tolerated the radiotherapy well with no complications experienced at last follow-up. In addition, all patients had improvement in most of the signs or symptoms of GO. Ocular pain, palpebral edema, ocular motility and visual acuity improved in all patients. Diplopia improved in 2/10 patients, photophobia improved in 4/5 patients, ocular grittiness improved in 6/7 patients, ocular itching improved in 5/6 patients, conjunctival hyperemia improved in 10/11 patients, and tearing improved in 12/13 patients. Ocular itching and photophobia were not statistically improved. There was no difference in clinical effect between the 2 groups of patients. Prior to treatment 27 eyes were classified as active based on the CAS. Following treatment only 1 eye was reported to be active. The MRI findings also demonstrated improvement following radiotherapy in terms of a decrease in proptosis (13/32 patients) and decrease in thickness of the extraocular muscles. However, there was no difference detected between the 2 groups.
There are several limitations of the study that future larger studies of this kind will need to address to validate the results reported. This was a very short term follow-up study with a limited number of patients enrolled. Patients were not randomized and the reason for the corticosteroid treatment in the 9 patients is not clear. Also it is not clear if the clinical assessment of the patients was conducted in a masked fashion. A comparator arm composed of patients receiving standard dose radiotherapy was not included in the study to detect the possible benefit of protracted hypofractionated radiotherapy.

**CME ANSWERS**

1. **c**
2. **a**
3. **a**

**REFERENCES**

LEARNING OBJECTIVES

1. Become familiar with recent risk estimates for progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis (MS) receiving natalizumab
2. Understand the efficacy and safety data concerning fingolimod, a recently approved oral medication for MS
3. Become familiar with several oral and infusion investigational agents for MS currently in phase 3 clinical trials

CME QUESTIONS

1. What is the approximate risk of developing PML for an MS patient treated with natalizumab who has positive JC virus serology, has received prior immunosuppression, and has received natalizumab for greater than 2 years?
   a. .1%
   b. 1%
   c. 10%
   d. 50%

2. What is the reported incidence of macular edema in patients receiving fingolimod 0.5mg (without a history of diabetes or uveitis)?
   a. .04%
   b. .4%
   c. 4%
   d. 40%

3. Dimethyl fumarate is related to a compound that is licensed in Europe to treat what condition?
   a. Rheumatoid arthritis
   b. Psoriasis
   c. Crohn’s disease
   d. Myasthenia gravis

KEYWORDS

1. Multiple Sclerosis
2. Natalizumab
3. Fingolimod
4. Progressive Multifocal Leukoencephalopathy

INTRODUCTION

Recent progress makes it clear that we are in a new era regarding therapeutics for multiple sclerosis (MS). After a long history of treating MS symptomatically, the past two decades have brought a new armamentarium of disease-modifying therapies that modulate the autoimmune response in a variety of ways. The clinician may now select from 8 medications approved for MS by the US Food and Drug Administration! Between 1993 and 2004, the main platform medications were injectable (either subcutaneous or intramuscular), but recently approved agents utilize intravenous and oral delivery routes [1, 2]. These factors can have a major impact on patient convenience and adherence. The clinical data regarding these developments are of great importance to the treating neurologist, who will be charged with balancing the risks and benefits of newly approved therapies in aiming to select appropriate choices for the patient. This syllabus will review clinical data regarding MS therapies that have been recently approved or are currently in phase 3 clinical trials.

RECENTLY APPROVED AGENTS

NATALIZUMAB

Natalizumab (Tysabri®, Biogen Idec and Elan) is a humanized monoclonal antibody that interrupts leukocyte trafficking by blocking the interaction between leukocyte α4 integrins and endothelial receptors. The efficacy of natalizumab was originally reported in two phase 3 clinical trials, AFFIRM and SENTINEL [3, 4]. In AFFIRM, 942 patients were randomized to receive natalizumab or placebo for 2 years. Compared to placebo, the group receiving natalizumab showed a 68% reduction in clinical relapse rate (p<0.001) and 42% reduction in risk of sustained disability in that time period (HR 0.58; 95% CI 0.43–0.77). Analysis of magnetic resonance imaging (MRI) scans obtained during the study demonstrated an 83% reduction in new or enlarging T2 lesions (p<0.001) and 92% reduction in gadolinium-enhancing lesions (p<0.001).

In SENTINEL, 1171 patients were randomized to receive natalizumab or placebo for 2 years. Compared to placebo, the group receiving natalizumab showed a 68% reduction in clinical relapse rate (p<0.001) and 42% reduction in risk of sustained disability in that time period (HR 0.58; 95% CI 0.43–0.77). Analysis of magnetic resonance imaging (MRI) scans obtained during the study demonstrated an 83% reduction in new or enlarging T2 lesions (p<0.001) and 92% reduction in gadolinium-enhancing lesions (p<0.001).

In SENTINEL, 1171 patients were randomized to interferon β-1a intramuscular once a week with either natalizumab or placebo. Patients receiving natalizumab demonstrated a reduced relapse rate compared to those receiving placebo (34% vs. 75%, p<0.001) and were less likely to have sustained disability progression (23% vs. 29%; p=0.02). This study was terminated 1 month early, however, because 2 study patients in the natalizumab arm developed progressive multifocal leukoencephalopathy (PML).
Natalizumab was originally approved by the FDA in 2004, but then withdrawn from the market in 2005 because of the occurrence of PML in 3 patients treated with the drug. In 2006 it was brought back to market with a black-box warning regarding the risk of PML. Post-marketing surveillance programs were initiated to address concerns regarding the incidence of PML in this population. These data have recently been analyzed to provide updated risk estimates for PML in patients with MS receiving natalizumab [5]. Among 99,571 patients treated with natalizumab (209,123 patient-years), 212 confirmed cases of PML were identified. Of these, 46 (22%) died; among the survivors with adequate follow-up data, 40% had severe disability. The over-all risk of PML was approximately 1/1000 patient-years, with a majority of cases occurring beyond 2 years of treatment.

The authors of this study (all employees of Biogen Idec) evaluated the utility of an anti-JC virus antibody assay to predict the risk of PML in patients treated with natalizumab [5]. The studies used the STRATIFY JC virus™ assay, which was developed by Biogen Idec and licensed to Quest Diagnostics’ Focus Laboratory. Where it is allowable, Biogen Idec and Quest have made this assay available for free to MS patients. The 2-step antibody assay uses an ELISA screening test and, when necessary, a confirmatory supplemental inhibition assay; while retaining good specificity, this method has higher sensitivity than prior PCR-based tests for JC virus DNA, which are only effective when the virus is actively replicating and shedding [6]. Test characteristics of this JC virus antibody assay were recently evaluated in the STRATIFY-1 and TYGRIS surveillance studies for patients receiving natalizumab [7]. Based on comparison to urinary JC virus DNA PCR results, the JC virus antibody assay was found to have a false negative rate of approximately 2.7%. Overall JC virus seroprevalence was estimated to be 54%; the value correlated with age and female gender, but was independent of the duration of natalizumab therapy.

In the recent investigation, stratified risk estimates for PML were calculated based upon 54 natalizumab-treated patients with PML who had undergone baseline JC virus antibody testing [5]. The analysis revealed that 100% of these patients had a positive JC virus antibody assay (compared to the estimated 54% seroprevalence in patients without PML) [7]. According to the authors’ calculations, negative JC virus status conferred an estimated risk of PML of <0.09% (95%CI 0–0.48). However, with combined positive JC virus status, prior immunosuppressant use, and greater than 24 months of natalizumab use, the estimated risk increases more than 100-fold to 11.1% (95%CI 8.3–14.5). Positive JC virus status associated with prior immunosuppressant use or greater than 24 months of natalizumab exposure (but not both) confers an intermediate risk of PML (between 0.56 and 4.6%). The FDA now recommends using JC virus antibody ELISA testing for all patients in whom treatment with natalizumab is being considered [8]. Periodic re-testing for JC virus antibodies will be an important way to detect new exposures (or false-negative results), but the optimal frequency of re-testing remains to be determined.

**FINGOLIMOD**

Fingolimod (Gilenya®, Novartis) is an oral sphingosine-1 phosphate 1 receptor analogue that causes internalization and downregulation of S1P, leukocyte receptors, preventing the egress of leukocytes from lymph nodes [10]. In 2010, following reports from two large phase 3 clinical trials (FREEDOMS and TRANSFORMS), fingolimod became the first oral drug approved by the FDA for use in MS [11, 12]. In FREEDOMS, 1272 patients were randomized to receive oral fingolimod (at a dose of either 0.5mg or 1.25 daily) or oral placebo. Patients receiving the 0.5mg dose of fingolimod, compared to those receiving placebo, demonstrated a 54% reduction in relapse rate (0.18 vs 0.40, p<0.001) and 17.7% reduction in risk of disability progression (HR 0.70; 95%CI 0.52–0.96). In TRANSFORMS, 1292 patients were randomized to receive either intramuscular interferon β1a weekly or fingolimod 0.5mg daily. Patients receiving fingolimod demonstrated a 52% reduction in risk of relapse rate (0.16 vs 0.33; p<0.001), although this 1 year study did not demonstrate a significant reduction in disability scores. Reported side effects from these trials (including deaths related to infection) were greater with the 1.25mg dose, and only the 0.5mg dose has been approved for clinical use.

### TABLE 1. RISK OF PML AMONG PATIENTS WITH MS TREATED WITH NATALIZUMAB [ADAPTED FROM [9]]

<table>
<thead>
<tr>
<th>Anti JC virus status</th>
<th>Natalizumab exposure &gt;24 mos</th>
<th>Prior Immunosuppressant use</th>
<th>Estimated risk of PML (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>+/-</td>
<td>+/-</td>
<td>&lt;0.09 (0–0.48)</td>
</tr>
<tr>
<td>Positive</td>
<td>No</td>
<td>No</td>
<td>0.56 (0.36–0.83)</td>
</tr>
<tr>
<td>Positive</td>
<td>No</td>
<td>Yes</td>
<td>1.6 (0.91–2.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>No</td>
<td>4.6 (3.7–5.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>Yes</td>
<td>11.1 (8.3–14.5)</td>
</tr>
</tbody>
</table>
The potential systemic side effects of treatment with fingolimod likely relate to consequences of S1P1 inactivation in other tissues. Cardiac conduction defects including bradycardia and AV block occur in 1% of patients receiving 0.5mg fingolimod. Of note, post-marketing experience has identified syncope, transient asystole, and even unexplained death within 24hrs of the first dose. Recent changes to the full prescribing information, made in April 2012, now recommend monitoring patients for bradyarrhythmias for 6 hours following the first dose, including an electrocardiogram before and after the observation period. If abnormalities are present after 6 hours, continued observation or hospitalization for overnight telemetry should occur.

Patients with pre-existing cardiac disease, including QTC prolongation, should undergo evaluation by a cardiologist, and upon receiving the first dose of fingolimod they should be monitored with overnight telemetry. The drug is contraindicated in patients with a history of myocardial infarction, unstable angina, second- or third-degree heart block, stroke, transient ischemic attack, or decompensated heart failure in the previous 6 months.

Of particular relevance to neuro-ophthalmologists, some patients treated with fingolimod can develop macular edema (which may be either symptomatic or asymptomatic) [13]. At the 0.5mg dose of fingolimod in the TRANFORMS study, macular edema occurred in 2 patients (0.5%). It did not occur in any patients at that dosage in FREEDOMS. The package insert for fingolimod describes that the occurrence of macular edema is believed to be approximately 0.4%, but may increase to approximately 20% in the setting of diabetes or prior uveitis [14]. For this reason, a dilated ophthalmoscopic exam is recommended before and 3 months following the initiation of therapy. Symptomatic patients should be examined urgently; if macular edema is present, cessation of the drug should be strongly considered. NANOS and the AAO have recently released a joint consensus statement advising routine eye examination at the onset of therapy and following 3–4 months; macular OCT is suggested in patients with abnormalities on exam or unexplained decreased acuity [15].

**INVESTIGATIONAL AGENTS IN CLINICAL TRIAL**

**DIMETHYL FUMARATE**

Dimethyl fumarate, also known as BG-12 (Panaclar®, Biogen Idec), is a fumaric acid ester that is believed to modulate the immune system by acting on oxidative pathways and stimulating anti-inflammatory cytokines. It is related to a drug that was licensed in Germany in 1995 (Fumaderm®, Biogen Idec) to treat psoriasis. In the DEFINE trial, 1234 patients were randomized to receive placebo or 240mg dimethyl fumarate twice daily or three times daily [16]. Patients receiving the drug demonstrated a 49% reduction in relapses (p<0.0001) and 38% reduction in disability progression (p=0.012) over the 2 year study. In addition, there was an 85% reduction in new or enlarging T2 lesions (p=0.0001) and 73% reduction in gadolinium enhancing lesions (p=0.0001). Reported adverse effects included transaminitis, nausea, diarrhea, and flushing. Based upon these data, dimethyl fumarate has been fast-tracked for expedited FDA regulatory review.

**LAQUINIMOD**

Laquinimod (Teva) is another orally administered drug; it is thought to have a number of immunomodulatory effects (including downregulation of MHC class II transcription factors and activation of anti-inflammatory cytokines). Conflicting results have arisen from the ALLEGRO and BRAVO trials. In the ALLEGRO study, 1106 patients were randomized to receive placebo or 0.6 mg laquinimod daily; patients receiving laquinimod demonstrated a 23% reduction in relapse rate in relapse rate (0.30 vs 0.39, p=0.002) and 29% reduction in disability progression (11.1% vs 15.7%; HR 0.64 95%CI 0.45–0.91) as well as a 37% reduction in new gadolinium enhancing lesions (p=0.012) [17]. In the BRAVO study, 1331 patients were randomized to laquinimod 0.6mg daily or intramuscular interferon β1a weekly. This study did not demonstrate a significant difference in relapse rate between groups, although the results may have been confounded by dissimilar levels of baseline disease activity judged by MRI [18]. Reported adverse side effects included transaminitis. Rates of herpes virus infection and cancers were similar in patients receiving drug and placebo. FDA approval of laquinimod is on hold until additional data are acquired.

**TERIFLUNOMIDE**

Teriflunomide (Aubagio®, Genzyme) is an oral drug that suppresses the immune system by inhibiting dihydroorotate dehydrogenase and suppressing synthesis of DNA pyrimidine bases. In the recent TEMSO trial, 1088 patients were randomized to receive either oral teriflunomide (7mg or 14mg daily) or placebo. Patients receiving 14mg teriflunomide demonstrated a 31% reduction in annualized risk of relapse (0.37 vs 0.54, p<0.001) and 30% reduction in risk of disability progression (20.2% vs. 27.3%, p=0.03) [9]. Reported serious adverse effects included nasopharyngitis, diarrhea, transaminitis, and hair thinning. Related compounds are reported to have teratogenic side effects (pregnancy category 4) that may limit its use. Additional phase 3 trials of teriflunomide versus interferon or placebo are being conducted. In addition, TOPIC is a phase 3 trial assessing teriflunomide versus placebo in patients with a clinically isolated syndrome (CIS) [19].

**ALEMTUZUMAB**

Alemtuzumab (Campath®, Genzyme) is a humanized monoclonal antibody that binds to CD52, a receptor found on both B and T lymphocytes. It is approved for treatment of B-cell chronic lymphocytic leukemia (B-CLL) and produces marked immunosuppression lasting up to 16 months. Two phase 3 trials are ongoing. In the CARE MS1 trial, 581 treatment-naïve patients were randomized to receive alemtuzumab or SQ IFN β1a; patients receiving alemtuzumab demonstrated a 55% decrease in relapse rate but did not demonstrate a significant reduction in rate of disability progression [20]. Data have not yet been reported.
from another phase 3 trial of alemtuzumab (CARE MS2), which is studying patients who have relapsed on platform therapy. An increased risk of infections and autoimmune conditions, including thyroid dysregulation and immune thrombocytopenic purpura (ITP), are reported to occur [21].

**DACLIZUMAB**

Daclizumab (Zenapax®, Roche) is a monoclonal antibody that blocks IL-2 receptors on activated T cells. It has FDA approval for organ transplant patients. The phase 3 DECIDE trial is currently underway to evaluate its efficacy in MS (against IFN-β) [22].

**OCRELIZUMAB**

Ocrelizumab (Roche and Biogen Idec) is the humanized version of the monoclonal antibody rituximab, which produces B cell depletion by targeting the CD20 cell surface epitope. Reported adverse side effects in phase 2 studies included one death from a systemic inflammatory response with brain edema [23]. The drug is currently being studied in the ORCHESTRA phase 3 trials for use in MS [24].

**CONCLUSIONS**

We are in the midst of a revolution in MS therapeutics, with a number of promising newly approved and investigational disease-modifying agents. It is important for the treating neurologist to be aware of the clinical data regarding these therapies, in order to understand the balance between their clinical efficacy and toxicity. Most patients with newly diagnosed demyelinating disease will be best served by a platform immunomodulating therapy, including the interferons and glatiramer acetate; these agents have well-established safety profiles. However, for certain patients it may be reasonable to consider the newer agents reviewed in this syllabus. Relevant factors may include poor clinical or radiographic response to a platform therapy or an aggressive disease course at onset. For some patients with poor adherence to a platform therapy requiring frequent injections, a newer oral or infusion therapy may be a reasonable alternative, although the risks of this approach merit careful consideration. Continued detailed safety monitoring of these drugs is imperative to develop a more thorough understanding of their safety profiles, in support of balanced clinical decision making.

**TABLE 2. NEW AND EMERGING THERAPIES FOR MS**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Administration</th>
<th>Reported side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APPROVED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab (Tysabri®, Biogen Idec and Elan)</td>
<td>300mg iv every 28days</td>
<td>PML, headache, fatigue, UTIs, hypersensitivity reaction</td>
</tr>
<tr>
<td>Fingolimod (Gilenya®, Novartis)</td>
<td>0.5 mg po qd</td>
<td>Macular edema, bradycardia, shingles, skin cancer</td>
</tr>
<tr>
<td><strong>INVESTIGATIONAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate (BG-12, Biogen)</td>
<td>120–240mg po tid</td>
<td>Diarrhea, nausea, cramps, transaminitis</td>
</tr>
<tr>
<td>Laquinimod (Teva)</td>
<td>0.6mg po qd</td>
<td>Transaminitis</td>
</tr>
<tr>
<td>Teriflunomide (Genzyme)</td>
<td>7–14 mg po qd</td>
<td>Headache, diarrhea, nausea, back pain, transaminitis, nasopharyngitis, UTI</td>
</tr>
<tr>
<td>Alemtuzumab (Campath®, Genzyme)</td>
<td>12–24mg qd x5d iv once/year</td>
<td>ITP, thyroid dysfunction, headaches</td>
</tr>
<tr>
<td>Daclizumab (Zenapax®, Roche)</td>
<td>2mg/kg SQ every other week</td>
<td>Rash, lymphadenopathy, transaminitis, diarrhea</td>
</tr>
<tr>
<td>Ocrelizumab (Roche and Biogen Idec)</td>
<td>600–2000mg iv</td>
<td>Systemic inflammatory response</td>
</tr>
</tbody>
</table>
CME ANSWERS
1. c
2. b
3. b

REFERENCES
23. Kappos, L., D. Li, and P. Calabresi, Ocrelizumab in relapsing-remitting multiple sclerosis: 49 week efficacy and safety results of a phase 2 randomized placebo controlled multicenter trial,, in American Academy of Neurology (AAN) 63rd annual meeting2011: Honolulu, HI.
LEARNING OBJECTIVES

1. At the end of this lecture, the attendee will be able to identify major changes in acute stroke treatment
2. At the end of this lecture, the attendee will be able to name approved stroke prevention options besides warfarin for those with atrial fibrillation
3. At the end of this lecture, the attendee will be able to discuss the role of both CEA and stenting for carotid stenosis

CME QUESTIONS

1. During what additional time window is IV alteplase frequently given in the US, even though it is not yet FDA approved?
   a. 0–3 hours
   b. 3–4.5 hours
   c. 4.5–6 hours
   d. 6–9 hours
   e. 9–12 hours
2. Which other medications are FDA approved for stroke prevention in atrial fibrillation as alternatives to warfarin?
   a. Apixaban
   b. Dabigatran
   c. Rivaroxaban
   d. Only b and c
   e. None of the above
3. In patients with internal carotid stenosis of >50%, CREST demonstrated that
   a. CEA is superior to stenting
   b. Stenting is superior to CEA
   c. CEA and stenting are equal
   d. Neither CEA nor stenting are appropriate treatment options
   e. CEA and stenting are superior to medical management

KEYWORDS

1. Acute Stroke
2. Atrial Fibrillation
3. Carotid Stenosis
4. Intracranial Arteriosclerosis
5. Patent Foramen Ovale

ACUTE STROKE TREATMENT

MEDICAL MANAGEMENT

Intravenous thrombolysis with alteplase (Genentech; San Francisco, CA) is the only FDA approved treatment for acute ischemic stroke when administered fewer than 3 hours after the onset of symptoms. The European Cooperative Acute Stroke Study-III (ECASS III) investigators tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke. After excluding patients with intracranial hemorrhage or major ischemic stroke, patients were randomized in a double-blind fashion to receive treatment with intravenous (IV) alteplase or placebo. The primary end point was disability at 90 days with either a favorable outcome (modified Rankin Scale [mRS] 0-1) or unfavorable outcome (mRS 2-6). The secondary end point was a global outcome assessment combining 4 neurologic and disability scores. Safety outcomes included death, symptomatic intracerebral hemorrhage (ICH), and other serious adverse events.

821 patients were enrolled in the study, with 418 assigned to the alteplase/treatment group and 403 to the placebo group. The median time for drug administration was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; OR, 1.34; 95% CI 1.02 to 1.76; P = 0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio [OR], 1.28; 95% CI, 1.00 to 1.65; P<0.05). The rate of ICH was higher with alteplase than with placebo (for any ICH, 27.0% vs. 17.6%; P = 0.001; for symptomatic ICH, 2.4% vs. 0.2%; P = 0.008). Mortality did not differ between the alteplase and placebo groups (7.7% and 8.4%; P = 0.68), and there was no difference in the rates of other serious adverse events.
Following the results of the ECASS III trial, a pooled analysis of data from 8 double blind randomized control trials (RCTs) evaluating alteplase for acute stroke was conducted. This meta-analysis of 3670 patients revealed that the OR for a good outcome (mRS 0–1) at 90 days was 1.3 (P = 0.01) for those treated with IV alteplase in the 3 to 4.5 hour window. Mortality was increased for those treated with alteplase beyond 4.5 hours (OR 1.5, P = 0.05). The investigator’s conclusions stated, “patients with ischemic stroke selected by clinical symptoms and CT [computed tomography] benefit from intravenous alteplase when treated up to 4.5 hours. To increase the benefit to a maximum, every effort should be taken to shorten delay in initiation of treatment. Beyond 4.5 hours, risk might outweigh benefit.” Currently, the International Stroke Trial III has randomized patients to IV alteplase vs. placebo treated 0 to 6 hours from time last seen normal, with the results most likely becoming available sometime in 2012. Treatment with alteplase in the 3 to 4.5 hour window is supported by the American Heart Association, the Canadian Best Practice Guidelines, and the European Stroke Organisation (ESO). Although not approved by the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA), treatment within 3 to 4.5 hours is currently practiced in much of Europe and the United States. Some concern exists that the longer time window provides an opportunity to delay treatment, although the available data would suggest that earlier treatment provides greater benefit of therapy and rapid treatment protocols should be encouraged.

More restricted eligibility criteria were used in the ECASS III trial, with some additions and modifications to those typically used for alteplase administration within the 3 hour window, and these should be used when treating patients in the 3–4.5 hour window (additions and modifications underlined below).1

- Age < 18 years, > 80 years
- NIHSS score ≥25 or > 1/3 MCA territory on imaging
- Evidence of ICH on CT or suspicion of subarachnoid hemorrhage (SAH)
- Stroke, major surgery or trauma, acute pancreatitis, documented ulcerative gastrointestinal (GI) disease within last 3 months
- Prior disabling stroke (mRS ≥2) and diabetes requiring treatment
- Arterial puncture at non-compressible site, lumbar puncture, heart massage, obstetrics delivery within 10 days
- Uncontrolled hypertension at time of treatment (> 185 mmHg SBP or > 110 mmHg DBP) or aggressive treatment needed to lower BP (> 1 dose IV medication)
- Prior ICH, central nervous system (CNS) neoplasm, arteriovascular malformation, aneurysm, CNS damage, intracranial/spinal surgery, or esophageal varices
- Active internal bleeding, recent severe bleeding, or known bleeding diathesis including but not limited to:
  - Receiving oral anticoagulation regardless of international normalized ratio (INR)
  - Received heparin within last 48hr and elevated aPTT
  - Platelet count < 100,000/mm3
  - Glucose < 50 mg/dL or > 400mg/dL
  - Seizure at onset of stroke
  - Gl or genitourinary (GU) bleeding within 21 days
  - Minor neurological deficit (not detectable on NIHSS)
  - Rapidly improving stroke symptoms
  - Hemorrhagic retinopathy
  - Major disorder with increased bleeding risk (eg-pericarditis, bacterial endocarditis, severe liver disease)

SURGICAL / INTERVENTIONAL MANAGEMENT
Most comprehensive stroke centers worldwide routinely are performing intra-arterial (IA) stroke thrombolysis using clot retrieval devices, employing these devices in approximately 65% of IA interventions. The annual number of IA stroke interventions in the United States is estimated to be between about 10,000 and 40,000. The Stroke Warning Information and Faster Treatment Study (SWIFT) examined the efficacy and safety of the Solitaire™ FR revascularization stent and clot retriever device (Covidien / ev3 Endovascular; Plymouth, MN) compared with the Merci® clot retriever (Concentric Medical Inc.; Mountain View, CA) as initial device therapies. This trial was a multicenter, randomized, active comparator, and importantly, non-inferiority trial and preliminary results were reported at the 2012 American Heart Association International Stroke Conference and published in August 2012. The primary end point was successful recanalization in all treatable vessels, without symptomatic ICH (SICH) and without rescue therapy. The secondary end points were good neurological outcome defined as mRS ≤ 2, or equal to the prestroke mRS if the prestroke mRS was higher than 2, or NIHSS score improvement ≥ 10, mortality, and serious adverse events at 90 days. All clinically adverse, technical and procedural events were adjudicated by an independent clinical events committee. A core lab blinded to treatment assignment provided independent angiographic, CT and MRI evaluations.

One hundred and forty four patients were enrolled in the study from 18 sites, with 58 assigned to the Solitaire™ group and 55 to the Merci® group. Successful recanalization was achieved in 60.7% with Solitaire™ and 24.1 with Merci®. More patients had a good outcome with Solitaire™ than with Merci® at 90 days (58.2% vs. 38.3%; P = 0.0001 for superiority and < 0.017 for non-inferiority). Mortality was lower in the Solitaire™ group (17.2% and 38.2%; P = 0.0001 for superiority and < 0.02 for non-inferiority).
STROKE PREVENTION AND RECOVERY

MEDICAL MANAGEMENT

Oral Factor Xa inhibitors and direct thrombin inhibitors for atrial fibrillation

Warfarin, a vitamin K antagonist, has been the standard oral anticoagulant for over 5 decades, but the need for frequent INR monitoring, dosage adjustments, multiple drug interactions, and a narrow therapeutic window have inspired the research and development of new oral agents. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, 18,113 atrial fibrillation patients with at least 1 additional stroke risk factor were randomly assigned to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or adjusted dose warfarin with a target INR 2–3. Dabigatran (Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT) is an oral direct thrombin inhibitor. Patients were followed for a mean of 2 years at 951 sites in 44 countries. The dabigatran was administered in a double-blind fashion, while warfarin was given open-label. Participants were an average age of 71 years and 64% were men. Half of the patients had previously used warfarin, 20% has suffered a prior stroke / transient ischemic attack, and 20% used aspirin <100 mg daily during the course of the trial. The time in the therapeutic range for warfarin patients averaged 64%.

Dabigatran 150 mg twice daily was superior to warfarin for the outcomes of all stroke or systemic embolism, all stroke, and all-cause mortality, and was associated with a similar risk of major hemorrhage. Dabigatran 110 mg twice daily resulted in trends toward lower rates for these outcomes compared with warfarin without achieving statistical significance, but had a significantly lower rate of major hemorrhage. ICH was significantly lower with both dabigatran doses. No major hepatotoxicity was reported, but dyspepsia was more frequent in those assigned to dabigatran.

There is currently no clear means to reverse the anticoagulant effects of dabigatran emergently in case of major hemorrhage, although it has a relatively short half-life and can be partly removed through hemodialysis. P-glycoprotein inhibitors such as verapamil, amiodarone, and quinidine interact with dabigatran. One estimate suggests that the effects of warfarin and dabigatran for stroke prevention are approximately equal when the time spent in therapeutic range for warfarin is >70%.

Unfortunately, INRs are infrequently well controlled in clinical practice. Dabigatran has been included in an American Heart Association/American College of Cardiology practice guideline as an alternative to warfarin for atrial fibrillation patients.

The phase III randomized Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial compared apixaban (Bristol Myers Squibb; New York, NY. Pfizer; New York, NY), a novel oral selective, reversible, direct factor Xa inhibitor, with aspirin for prevention of thrombotic events in patients with atrial fibrillation. The study included 5999 atrial fibrillation patients at 522 international sites with at least 1 additional stroke risk factor who were not thought to be candidates for warfarin. Patients were randomized, double-blind to apixaban 5 mg twice daily vs. once daily aspirin 81–325 mg daily. Exclusion criteria included recent serious bleeding, active peptic ulcer disease, and severe renal insufficiency. Average participants were 70 years old, 59% men, 14% with prior stroke or TIA, and 9% in both groups took additional non-study aspirin during the follow-up period. The trial was terminated early after an interim analysis at a mean follow-up of 1.1 years found a larger than expected benefit of apixaban over aspirin.

Both ischemic strokes and ICH were reduced by apixaban over aspirin (HR 0.46, 95% CI 0.33-0.65, P <0.001) with an absolute benefit of 1.8% per year. The rate of major bleeding was slightly decreased in the apixaban group (1.4% per year) compared to 1.2% per year with aspirin (HR 1.13, 95% CI 0.74-1.75) but did not achieve statistical significance. There were 11 ICH with apixaban compared to 13 with aspirin.

Some caution is necessary when interpreting the positive results of AVERROES. While major hemorrhage appears slightly lower with apixaban over aspirin, the hazard ratio is accompanied by a relatively broad confidence interval. Drugs metabolized through the CYP450 system may interact with apixaban, and other interactions may not have been identified during the trial period. Apixaban has not yet been approved by the FDA.

Apixaban was simultaneously compared to warfarin for the prevention of thrombotic events in patients with atrial fibrillation in the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial. In this double-blind, noninferiority, RCT, the investigators compared apixaban at a dose of 5 mg twice daily with warfarin, target INR 2-3. Secondary objectives included testing for superiority with respect to the primary outcome and to the rates of major bleeding and all cause mortality. The study included 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome included ischemic stroke, ICH, or systemic embolism. Median follow-up was 1.8 years.

The rate of ischemic stroke, ICH, or systemic embolism was 1.27% per year in the apixaban group, as compared with 1.60%/year in the warfarin group (HR 0.79; 95% CI 0.66–0.95; P<0.001 for noninferiority; P = 0.01 for superiority). The rate of major bleeding was 2.13%/year in the apixaban group, as compared with 3.09%/year in the warfarin group (HR 0.69; 95% CI, 0.60=0.80; P<0.001), and the rate of all cause mortality was 3.52% and 3.94%, respectively (HR 0.89; 95% CI, 0.80-0.99; P = 0.047). The rate of ICH was 0.24%/year in the apixaban group, as compared with 0.47%/year in the warfarin group (HR 0.51; 95% CI, 0.35-0.75; P<0.001), and
The rate of ischemic or uncertain type of stroke was 0.97%/year in the apixaban group and 1.05%/year in the warfarin group (HR 0.92; 95% CI, 0.87-0.96; P = 0.001). Again, caution is necessary when interpreting the results of ARISTOTLE for many of the same reasons described regarding AVERROES.

The Rivaroxaban-once daily (Janssen; Titusville, NJ), oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was designed to compare rivaroxaban with warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke. In this double-blind, noninferiority, RCT, the investigators enrolled 14,264 patients with atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban 20 mg daily or warfarin. The primary end point was stroke or systemic embolism.

Stroke or systemic embolism occurred at a rate of 1.7%/year in the rivaroxaban group 2.2%/year in the warfarin group (HR 0.79; 95% CI 0.66-0.96; P<0.001 for noninferiority). In the intention-to-treat (ITT) analysis, the primary end point occurred at a rate of 2.1%/year in the rivaroxaban group and 2.4%/year in the warfarin group (HR, 0.88; 95% CI, 0.74-1.03; P<0.001 for noninferiority; P = 0.12 for superiority). The rate of major and nonmajor bleeding was 14.9%/year for rivaroxaban and 14.5% /year for warfarin (HR 1.03; 95% CI, 0.96-1.11; P = 0.44), with significant reductions in subgroup analysis for ICH (0.5% vs. 0.7%, P = 0.02) and fatal bleeding (0.2% vs. 0.5%, P = 0.003) in the rivaroxaban group.

Should oral Factor Xa inhibitors and direct thrombin inhibitors replace warfarin for antithrombotic prophylaxis for patients with atrial fibrillation and if so, which agent is first line? Comparing the risk reductions seen in their phase III trials versus warfarin, all of the trials demonstrated similar reductions in stroke or systemic embolism (dabigatran 110 mg BID, rivaroxaban) or superior efficacy (dabigatran 150 mg BID, apixaban) versus warfarin. The rate of major bleeding was significantly lower with apixaban versus dabigatran 150 mg BID (HR 0.74, 95% CI 0.61-0.91) and rivaroxaban (HR 0.66, 95% CI 0.54-0.81). Major bleeding was similar comparing apixaban and dabigatran 110 mg BID. The patient populations in the trials of the three drugs were generally similar, but there were important differences, complicating this type of head-to-head study comparison. RE-LY and ARISTOTLE patient populations were of similar age, gender, and enrollment stroke risk, but ROCKET-AF included slightly older patients and who had a higher stroke risk. Additionally, RE-LY and ARISTOTLE patients had experienced prior stroke, TIA, or systemic embolism in about 20% of enrollees, but about 55% of the ROCKET-AF patients had a similar history. The time spent in the therapeutic range averaged 64% for the warfarin group in RE-LY, 62% for ARISTOTLE, and 55% for ROCKET-AF. Only dabigatran and rivaroxaban are currently FDA approved for antithrombotic treatment in atrial fibrillation. All of these comparisons should be approached with caution, given differences in the patient populations, outcome definitions and study methodology. Clinicians are probably still best served by using the primary data from the trials and the established FDA indications when choosing an agent for thrombotic prophylaxis in atrial fibrillation.

Glycemic control

Intensive glycemic control has demonstrated increased mortality among those with type 2 diabetes mellitus (DM) and a high cardiovascular disease risk. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial examined the 5-year outcomes of intensive glycemic control on mortality and important cardiovascular events. Ten thousand one hundred and eight patients with type 2 DM and cardiovascular disease or additional risk factors received either intensive treatment with a glycosylated hemoglobin level below 6.0% or standard treatment with a level of 7 to 7.9% for a mean of 3.7 years. Intensive therapy was terminated early due to excess all-cause mortality in the intensive-therapy group. The target glycosylated hemoglobin level was subsequently changed to 7 to 7.9% for all participants, who were then followed until trial until the completion of additional blood pressure and cholesterol control arms of the study. The primary outcome was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular death.

Before intensive treatment was discontinued, there were no significant differences between the two glucose control groups in the composite rate of nonfatal MI, nonfatal stroke, and cardiovascular death.

(P = 0.13), but subgroup analysis revealed increased all-cause mortality in the intensive group (HR 1.21; 95% CI 1.02-1.44) with interestingly fewer nonfatal MIs (HR 0.79; 95% CI 0.66-0.95). These patterns were seen during the entire trial follow-up (HR for mortality 1.19, 95% CI 1.03-1.38; and for nonfatal MI 0.82, 95% CI 0.70-0.96).

Vitamins for stroke prevention

Previous epidemiological studies had suggested that elevated plasma homocysteine might be a risk factor for major vascular events. The Vitamins to Prevent Stroke (VITATOPS) trial examined whether once-daily B vitamin supplements would lower homocysteine and reduce the vascular events in patients with recent stroke or TIA. In this parallel, double-blind RCT, patients with stroke or TIA within 7 months of enrollment from 123 medical centers in 20 countries received either placebo or B vitamins (folic acid 2 mg, vitamin B6 25 mg, and vitamin B12 0.5 mg) and were followed for a median of 3.4 years. The primary endpoint was a composite of stroke, MI, or vascular death evaluated by ITT.

Eight thousand one hundred and sixty-four patients received B vitamins or placebo. Fifteen percent of patients receiving B vitamins and 17% receiving placebo achieved the primary
endpoint, with an absolute risk reduction of 1.56% (95% CI–0.01 to 3.16 \( p=0.05 \)). There were no serious adverse reactions and no differences in common adverse reactions between the two groups. Although the vitamins used in the trial resulted in homocysteine lowering, with about a 2% risk reduction for each 1 \( \mu \text{mol/L} \) decrease in homocysteine, vitamin treatment was not more effective than placebo in reducing the stroke, myocardial infarction, and vascular death. There is still some controversy among vascular neurologists about the continued use of B vitamins for stroke prevention despite the results of this trial, due to the general safety of the supplements and the global health burden of stroke.

Selective serotonin reuptake inhibitors (SSRI) for motor recovery

Motor weakness is among the most common deficits caused by stroke, and few small clinical trials had suggested that fluoxetine improves motor recovery. The Fluoxetine for motor recovery after acute ischaemic stroke (FLAME) trial investigated whether fluoxetine would enhance motor recovery if given to patients with motor deficits soon after an ischemic stroke. This double-blind, RCT included patients from 9 stroke centers in France who suffered an ischemic stroke with hemiplegia / hemiparesis. Patients were assigned to fluoxetine 20 mg daily or placebo for 3 months starting 5 to 10 days after the onset of their stroke. All patients received rehabilitation therapy. The primary outcome was the change on the Fugl-Meyer motor scale (FMMS) between day 0 and day 90 after the start of the study drug.

One hundred and eighteen patients were randomized and 113 were included in the on-treatment analysis. Two patients died and three withdrew from the study after randomization and were not included in the “full set” analysis. FMMS improvement at day 90 was greater in the fluoxetine group (mean adjusted change of 34.0 points, 95% CI 29.7–38.4) than in the placebo group (24.3 points, 95% CI 19.9–28.7, \( p=0.003 \)). There were no differences in adverse events among the two groups.

Study limitations include the small number of included patients that did not represent the general stroke population. Treatment was stopped after 90 days so the long term treatment effect is unknown. Random error cannot be completely excluded, and the results need to be confirmed in a planned, larger RCT. However, some clinicians are already liberalizing their use of SSRIs in stroke patients given the clinically relevant effect of fluoxetine demonstrated in this trial.

SURGICAL / INTERVENTIONAL MANAGEMENT

Stenting for intracranial stenosis

Atherosclerotic intracranial arterial stenosis may be an important cause of stroke, and percutaneous transluminal angioplasty and stenting (PTAS) had been increasingly employed in an effort to prevent recurrent stroke. The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial compared PTAS to aggressive medical management to prevent recurrent stroke. Aggressive medical management for both groups included aspirin 325 mg daily, clopidogrel 75 mg daily for 90 days after enrollment, management of primary and secondary risk factors, including a lifestyle modification program. Blood pressure targets included SBP < 140 mm Hg (<130 mm Hg in diabetics), and the low-density lipoprotein (LDL) goal was less than 70 mg per deciliter (1.81 mmol per liter). This randomized trial assigned patients with recent TIA or stroke attributed to 70 to 99% stenosis of a major intracranial artery to aggressive medical management alone or aggressive medical management plus PTAS with the Wingspan™ stent system (Boston Scientific / Target; Natick, MA). The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure during the follow-up period, or stroke in the territory of the qualifying artery beyond 30 days. End points were adjudicated by independent neurologists and cardiologists who were masked to treatment assignments.

Enrollment was prematurely halted by the data and safety monitoring board (DSMB) due to increased rates of stroke or death in the PTAS group. Four hundred and fifty one patients underwent randomization, with a 30-day stroke or death rate of 14.7% in the PTAS group and 5.8% in the medical-management group (\( P = 0.002 \)). Beyond 30 days, there was no difference in stroke rates between the groups. Mean duration of follow-up was 11.9 months, although follow up for this study is still in progress. The likelihood of stroke beyond 30 days differed significantly between the two groups, with a 20% 1-year stroke rate in the PTAS group and 12.2% in the medical-management group (\( P = 0.009 \)).

One limitation of the trial was the inclusion of a cerebral angiography before enrollment, potentially prolonging the time to randomization compared to other trials. In addition, 25 of the 33 strokes in the PTAS group occurred ≤ 1 day after the procedure and 8 occurred 2–6 days later. This suggests that the rate of 30-day events with PTAS could be reduced with better patient selection and physician procedural experience.

Patent foramen ovale (PFO) closure

Controversy exists regarding the best treatment for patients with cryptogenic stroke and patent foramen ovale (PFO), with recommendations varying among antiplatelet therapy, anticoagulation, or either endovascular or open surgical PFO closure for stroke prevention. The Evaluation of the STARFlex® Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (CLOSURE II) trial examined occlusion of PFO in patients with cryptogenic ischemic stroke versus medical management for prevention of recurrent
stroke.16 Patients were ≤60 years of age, with cryptogenic stroke or TIA within 6 months and a PFO detected by transthoracic echocardiogram (TEE). Nine hundred and nine patients were enrolled from 87 North American sites, with a mean age of 46 years, 52% men, 72% with stroke rather than TIA as the qualifying event, and 36% with atrial septal aneurysm. Patients were randomized in an open label fashion to closure with the STARFlex® device (NMT Medical, Inc.; Boston, MA) followed by clopidogrel plus aspirin for 6 months then aspirin alone versus medical therapy chosen by the local investigator (warfarin, aspirin, or a combination of both). Repeat TEE after 6 months demonstrated continued PFO occlusion in 86% of the device patients.

No benefit in the PFO closure group was identified during the 2 year follow up. Stroke rates were less than 2% per year and about equal in both arms.16 Atrial fibrillation was identified more frequently in the PFO closure group.

The CLOSURE I results do not support the routine closure of PFOs in addition to antithrombotic medications for secondary prevention of stroke in those with cryptogenic stroke. Limitations of the study include a low rate of recurrent strokes, wide confidence intervals and inadequate statistical power to exclude an important benefit of the intervention group. Four additional trials examining PFO closure for stroke prevention are underway and may provide additional information to guide treatment decisions in this challenging patient population.

Carotid stenosis treatment

Carotid endarterectomy (CEA) was established as effective treatment for symptomatic and asymptomatic patients in previous randomized controlled trials. Carotid artery stenting (CAS) may be another treatment option. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) compared carotid endarterectomy (CEA) with carotid angioplasty / stenting using the Acculink® / Accunet devices (Abbott Vascular; Abbott Park, IL) for stroke prevention in patients with either symptomatic or asymptomatic carotid stenosis.17 Eligibility criteria included ≥ 50% stenosis on angiography, ≥ 70% ultrasonography, or ≥ 70% CT angiography or MR angiography. In 2005 eligibility was extended to asymptomatic patients, with more strict criteria including ≥ 60% stenosis on angiography, ≥ 70% on ultrasonography, or ≥ 80% CT angiography or MR angiography. Two thousand five hundred and two patients were enrolled from 108 US and 9 Canadian sites. The primary end point was a composite of stroke, MI, or all cause mortality within 30 days or any ipsilateral stroke within 4 years of randomization. About half of patients had symptomatic carotid artery stenosis ≥ 50%, and 86% of participants had ≥ 70% stenosis. There was a rigorous proficiency period to document the skill of operators performing the procedures. Patients had a mean age of 69 years, 65% men, 30% diabetic, 26% current smokers. The average blood pressure at enrollment was 141/74 mmHg. There was no difference in the 4-year rates of the primary end point between either group (7.2% for stenting and 6.8% for CEA, HR with stenting 1.11; 95% CI 0.81-1.51; P = 0.51). The rate of stroke or death was 6.4% with stenting and 4.7% with CEA (HR 1.50, P = 0.03) and were not significantly different between the symptomatic and asymptomatic groups. Rates of end point subgroups within 30 days differed between the stenting and CEA. After this periprocedural period, the rates of ipsilateral stroke with stenting and CEA were similar 2.0% and 2.4% respectively, P = 0.85. Mortality rates were 0.7% with stenting and 0.3% with CEA (P = 0.18). Stroke rates were 4.1% for stenting and 2.3% for CEA (P = 0.01) and MI rates were 1.1% with stenting and 2.3% with CEA (P = 0.03). MI may have been clinically silent and was diagnosed based on a creatine kinase MB fraction or troponin level that was twice normal or higher, in addition to either chest pain, symptoms consistent with ischemia or ECG evidence of ischemia, including new ST- segment depression or elevation.

In contrast, all strokes were clinically evident. When evaluating the subgroup of all strokes and death at 4 years, CEA was superior. There was no difference in treatment effects with gender or symptomatic status, but there was a significant interaction (P = 0.02) for age, with CEA demonstrating more benefit at older ages and stenting with greater efficacy at younger ages. Crossover was identified at an age of approximately 70 years. The investigators concluded that the risk of the primary outcome did not differ between the two groups, but the study may have been underpowered to determine a significant clinical benefit of either group given the wide CIs.

Vascular bypass

After a failed trial evaluating external carotid (EC)-internal carotid (IC) bypass surgery for stroke prevention in the 1990s, the Carotid Occlusion Surgery Study (COSS) examined whether EC-IC bypass surgery added to best medical therapy reduces recurrent ipsilateral ischemic stroke in patients with recently symptomatic internal carotid artery occlusion and hemodynamic evidence of cerebral ischemia.18 This was a parallel-group, randomized, open-label, blinded-adjudication clinical treatment trial conducted at 49 centers in the United States and Canada. Patients with angiographically confirmed internal carotid artery occlusion with hemispheric symptoms occurring within 120 days of enrollment and hemodynamic cerebral ischemia defined by ipsilaterally increased oxygen extraction fraction measured by PET. One hundred and ninety five patients were randomized. EC-IC bypass was conducted through anastomosis of a superficial temporal artery branch to middle cerebral artery branch. Antithrombotic therapy and risk factor management were recommended for all patients in accordance with established practice. The primary outcome was a composite of all stroke and death from surgery through 30 postoperative days and ipsilateral ischemic stroke within 2 years of randomization in the surgical arm. For patients...
not assigned to surgery or who did not receive surgery, the primary endpoint was the composite of all stroke and death from randomization through the first 30 days and ipsilateral ischemic stroke within 2 years of randomization.

The trial was terminated early by the DSMB due to a futility analysis. Rates for the composite end point were 21.0% (95% CI 12.8%-29.2%) for the surgical group and 22.7% (95% CI 13.9%-31.6%) for the nonsurgical group, an absolute difference of 1.7% (95% CI, –10.4%-13.8%). Thirty-day rates for ischemic stroke were 14.4% in the surgical group and 2.0% in the nonsurgical group, a difference of 12.4% (95% CI 4.9-19.9%).

Limitations of the study included a relatively small number of outcome events and the potential for bias at individual sites given that sham surgery was not performed. The 2 year recurrent stroke rate in the medical therapy arm is similar to that seen in 70% to 99% symptomatic carotid stenosis in the NASCET trial. The COSS investigators concluded that EC-IC bypass surgery provided no additional benefit over medical management for preventing subsequent ischemic stroke.

**SUMMARY**

For acute stroke treatment, alteplase given 3—4.5 hours after stroke onset benefits stroke patients at 90 days, but the benefit is less robust than earlier alteplase treatment and is not yet FDA approved. Intra-arterial therapies including newer clot retrieval devices provide hope for additional acute treatment options.

For stroke prevention and recovery, oral Factor Xa inhibitors and direct thrombin inhibitors appear equal to warfarin for stroke prevention in atrial fibrillation, and a few of these are FDA approved. Fluoxetine holds promise as a treatment for stroke prevention in atrial fibrillation, and a few of these new anticoagulants show promise for stroke prevention and recovery in specific populations.

Unfortunately, intense glycemic control, B vitamins, intracranial stenting, PFO closure, and EC-IC bypass all failed to demonstrate a benefit for stroke prevention.

**REFERENCES**

LEARNING OBJECTIVES

1. The attendee will be able to define chronic migraine.
2. The attendee will be able to know the current literature on OnabotulinumtoxinA for the current treatment of chronic migraine.
3. The attendee will be able to explain the current American Academy of Neurology/American Headache Society guidelines on treatment for episodic migraine prevention in adults.

ONABOTULINUMTOXINA IN CHRONIC MIGRAINE

Chronic migraine (CM) is defined as headache ≥ 15 days per month, of which at least eight headache days per month meet criteria for migraine without aura or respond to migraine-specific treatment (International Classification of Headache Disorders, second edition). Up to 5.1% of the general population suffers from this complication of migraine. CM is often disabling, interfering with work and school attendance. Treatment of CM can be very difficult, and is often complicated by overuse of pain medication.

OnabotulinumtoxinA is one treatment for chronic migraine. Improvement in migraine symptoms with botulinum toxin type A was first noted by a plastic surgeon in Los Angeles doing initial clinical trials of the toxin for wrinkles. The surgeon, W. J. Binder, contacted other colleagues, which eventually lead to an open-label study of the treatment of migraine. Improvement was seen in prevention of migraine and in treatment of acute attacks. Further studies did not show efficacy of onabotulinumtoxinA in episodic migraine or chronic tension-type headaches compared to placebo, but efficacy has been shown in chronic migraine.

The US Food and Drug Administration approved onabotulinumtoxinA for prophylactic treatment of chronic migraine in October 2010 based on two clinical trials conducted in the United States and Europe. The two studies are described below.

CME QUESTIONS

1. How many days per month must headaches be present to be considered chronic migraine?
   a. ≥ 10 days per month.
   b. ≥ 12 days per month.
   c. ≥ 15 days per month.
   d. ≥ 20 days per month.

2. True/False: OnabotulinumtoxinA is not effective for chronic migraine.

3. Which of the following medications have well-established efficacy in the prevention of migraine headaches (Level A in the American Academy of Neurology guidelines 2012)?
   a. Propranolol
   b. Lamotrigine
   c. Verapamil
   d. Topiramate

KEYWORDS

1. Chronic Migraine
2. OnabotulinumtoxinA
3. Botulinum Toxin Type A
4. Episodic Migraine Prevention
Why was the primary endpoint not met in PREEMPT 1?
In the discussion of the study it was pointed out that the onabotulinumtoxinA group had significantly fewer headache episodes, but longer cumulative headache duration, with a mean of > 20 cumulative headache hours per month than in the placebo group11. When the baseline imbalance was treated as an anomaly in the post hoc analysis, there was significant improvement in headache episodes in the onabotulinumtoxinA subjects.

The PREEMPT 2 trial was a phase 3 study, with a 24-week, double-blind, placebo-controlled phase, followed by a 32 week, open label phase12. The subjects were randomized to injections of onabotulinumtoxinA (155U-195U; n=347) or placebo (n=358) every 12 weeks for 2 cycles. The primary efficacy endpoint was the mean change in headache days per 28 days from baseline to weeks 21–24 post-treatment. OnabotulinumtoxinA was statistically superior to placebo in this regard and met the primary endpoint. All 5 secondary efficacy endpoints were also reached in the onabotulinumtoxinA group: frequency of migraine days, frequency of moderate/severe headache days, total monthly cumulative hours of headache occurring on headache days, proportion of patients with severe Headache Impact Test (HIT-6) scores, and frequency of headache episodes. The only treatment-related adverse events in the onabotulinumtoxinA group at a rate ≥5% were neck pain (7.5%) and muscular weakness (5.2%). Eyelid ptosis, myalgia, and musculoskeletal stiffness were also higher in the onabotulinumtoxinA group. The only serious adverse event in the onabotulinumtoxinA-treated group was a migraine requiring hospitalization. Discontinuation of treatment due to adverse events was 3.5% in the onabotulinumtoxinA group and 1.4% in the placebo group.

How does onabotulinumtoxinA compare to the other medications in treatment of chronic migraine? A multi-center double-blind pilot study published in 2011 compared onabotulinumtoxinA to topiramate in prevention of chronic migraine13. A total of 59 subjects were randomly assigned to topiramate plus placebo injections (n=30) and onabotulinumtoxinA plus placebo tablets (n=29). The active study period lasted 12 weeks. Up to 200 units of onabotulinumtoxinA were injected. Topiramate was started at 25 mg per day, then increased by 25 mg per week to a maximum of 200 mg per day. The primary endpoint was the Physician Global Assessment, a response to treatment using a 9-point scale:

-4 Clearance of signs and symptoms (about 100% improvement).
-3 Marked improvement (about 75% improvement).
-2 Moderate improvement (about 50% improvement).
-1 Slight improvement (about 25% improvement).
  0 Unchanged.
  -1 Slight worsening (about 25% worse).
  -2 Moderate worsening (about 50% worse).
  -3 Marked worsening (about 75% worse).
  -4 Very marked worsening (about 100% worse).

A positive treatment response was defined as +2 change in the Physician Global Assessment. Both the onabotulinumtoxinA and topiramate groups statistically improved with time, but there was no statistical difference between the 2 groups (both were equally efficacious). Equal efficacy was also shown in the multiple secondary endpoints that were explored: headache days, headache-free days, migraine disability assessment (MIDAS), headache impact assessment (HIT-6), and money spent on migraine medication.

In a study of botulinum toxin type A versus amitriptyline, both treatments were effective for chronic daily migraine14. However, in a study of botulinum toxin type A versus divalproex sodium, only the divalproex sodium decreased the number of headache days in the small number of chronic migraine patients in the study (n=7 in each group)15.

EPISODIC MIGRAINE PREVENTION IN ADULTS
In 2012, the American Academy of Neurology and the American Headache Society published revised guidelines for prevention of episodic migraine in adults16–18. The guidelines were issued for pharmacologic treatment, as well as non-steroidal anti-inflammatory drugs (NSAIDs) and complementary treatments. Only medications and complementary agents available in the United States were included in the analysis.

PHARMACOLOGIC AGENTS
Level A: Medications with established efficacy (≥2 Class I trials): Divalproex sodium, Sodium Valproate, Topiramate, Metoprolol, Propranolol, and Timolol. Frovatriptan for short term prophylaxis of menstrually-related migraine (MRM).

Level B: Medications are probably effective (1 Class I or 2 Class II studies): Amitriptyline, Venlafaxine, Atenolol, and Nadolol. Naratriptan and Zolmitriptan for MRM.

Level C: Medications are possibly effective (1 Class II study): Lisinopril, Candesartan, Clonidine, Guanfacine, Carbamazepine, Nebivolol, Pindolol, and Cyproheptadine.

Level U: Inadequate or conflicting data to support or refute medication use: Acetazolamide, Acenocoumarol, Coumadin, Picotamide, Fluvoxamine, Fluoxetine, Gabapentin, Protriptyline, Bisoprolol, Nicardipine, Nifedipine, Nimodipine, Verapamil, and Cyclandelate.

Other: Medications that are established as possibly or probably ineffective: Lamotrigine, Clomipramine, Acebutolol, Clonazepam, Nabumetone, Oxcarbazepine, and Telmisartan.

NSAIDS
Level A: None.

Level B: Fenaprofen, Ibuprofen, Ketaprofen, Naprofen, and Naproxen sodium.
5. Headache Impact Test (HIT-6)

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

For the above questions, choose one of the following: never, rarely, sometimes, very often, and always.

CME ANSWERS
1. c
2. False
3. a and d

REFERENCES

APPENDIX

Migraine Disability Assessment Scale (MIDAS)\textsuperscript{10, 21}

1. On how many days in the last 3 months did you miss work or school because of your headaches? (If you do not attend work or school, write “zero.”)
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school. If you do not attend school or work, write “zero.”)
3. On how many days in the last 3 months did you not do household work because of your headaches?
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days counted in question 3, where you did not do household work.)
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?
   A. On how many days in the last 3 months did you have a headache? (If headache lasted more than 1 day, count each day.)
   B. On a scale of 0–10, on average, how painful were these headaches? (Where 0 = no pain at all, and 10 = pain that is as bad as it can be.)

Headache Impact Test (HIT-6)\textsuperscript{20, 21}

1. When you have headaches, how often is the pain severe?
2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?
3. When you have a headache, how often do you wish you could lie down?
4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?
5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?


