CURRENT TREATMENT OF DIABETIC MACULAR EDEMA - LITERATURE REVIEW

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CURRENT TREATMENT OF DIABETIC MACULAR EDEMA (Abstract). Diabetic macular edema is the main cause of vision loss in developed countries among working people. Laser photocoagulation was the mainstay of treatment for many years, but it could only preserve visual acuity, and not increase it. The anti-VEGF (Vascular Endothelial Growth Factor) agents proved their efficacy in reducing macular thickness and increasing visual acuity, although a minority of patients (30%) achieved good visual acuity (20/40). Corticosteroids were most effective in reducing macular edema, but this reduction in macular thickness did not correlate with the level of visual acuity. They were associated with secondary cataract and glaucoma. Keywords: DIABETIC MACULAR EDEMA, LASER, ANTI-VEGF, CORTICOSTEROIDS.

Diabetic macular edema is a complication of diabetic retinopathy which involves the central part of the retina (macula) and it is the main cause of vision loss in developed countries among working people (1). This is why the socioeconomic consequences of this disease are very important, with significant implications for patients and healthcare providers (2).

Diabetic macular edema appears after the break-down of the blood-retinal barrier. Its incidence is directly correlated with the duration of diabetes and with poor glycemic control (3).

Chronic hyperglycemia produces a multifactorial cascade of biochemical processes including increased capillary permeability, activation of cytokines and inflammation, blood flow alteration. Vascular endothelial growth factor (VEGF), especially A-isoform, is a major factor in the stimulation of inflammation and also in angiogenesis (4). Hypoxia caused by microvascular alterations stimulates the production of VEGF to improve the capillary perfusion.

Neuronal dysfunction induced by hyperglycemia can also contribute to the drop of vision (5). Early diabetic neuropathy can be evaluated by Neuropad® test (6).

The aim of this review is to present the conclusions of the most important studies in the literature regarding this condition. Included in the analysis were only the prospective, comparative and randomized trials which included laser treatment, anti-VEGF agents and corticosteroids with a minimal follow-up of 6 months.

Laser photocoagulation
Laser photocoagulation was the main-
stay of treatment for diabetic macular edema. This was the conclusion of 2 major clinical trials: Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study (ETDRS).

Although photocoagulation was efficient in preserving visual acuity, it did not succeed to increase it. Patients with perifoveal ischemia are not considered eligible for this kind of therapy. Laser treatment can reduce the risk of moderate visual loss (defined as a drop of 3 lines on the visual acuity chart), by 50% but only 3% of the patients presented an increase in visual acuity (7).

Recent studies proved that laser photocoagulation resulted in an over 10 letter improvement in visual acuity in 7% to 31% of the cases (8).

This type of treatment for diabetic macular edema also has side effects. Foveal burns, visual field defects, subretinal fibrosis were reported after photocoagulation (9).

Despite aggressive treatment, some patients suffered a severe visual loss after the laser treatment (10).

**Intravitreal anti-VEGF agents**

*Ranibizumab* was the agent most frequently used in studies. There are 9 trials investigating the effect of this anti-VEGF agent in the treatment of diabetic macular edema.

*Ranibizumab for Edema of the Macula in Diabetes* (READ) 2 was the first important randomized clinical trial which compared the intravitreal injections with laser photocoagulation. After 6 months, the group treated with Ranibizumab visual acuity was significantly better than in the group treated with laser. Also, the addition of laser after Ranibizumab did not provide additional functional benefits (11).

*Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema* (REVEAL) was a similar study. It included 3 groups of patients who were treated with Ranibizumab, laser, or the combination Ranibizumab plus laser.

After 12 months of follow-up the results were better for the groups who received intravitreal injections in terms of improved visual acuity (12).

In the *Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema* (RESTORE) study the patients were also randomized to laser, Ranibizumab, and combined treatment. The results were analyzed after 12 months.

The group who received Ranibizumab had the best-corrected visual acuity. After 24 months of follow-up the outcomes were similar to those after 1 year of treatment (13).

These two studies proved a statistical significant improvement of visual acuity for the Ranibizumab patients compared to those who received laser treatment, especially when the variable analyzed was the proportion of patients who gained more than 15 letters on the visual acuity chart.

*Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus* (RISE and RIDE) studies were identical in design. They compared 2 doses of Ranibizumab (0.3 mg and 0.5 mg) with sham. After 24 months the proportion of patients who gained more than 15 letters was higher in the 0.3 mg group in RISE study, and in the 0.5 mg group in RIDE study. Both clinical trials showed better functional outcomes with Ranibizumab than with sham (14).
Ranibizumab for Edema of the Macula in Diabetes (READ 3) is another study which compared the outcomes of a high dose Ranibizumab (2 mg) with the standard dose (0.5 mg). After 6 months no statistically significant differences in visual acuity were found between the 2 groups (15).

Another study, published only in abstract form, compared monthly intravitreal injections with Ranibizumab (0.5 mg) versus Bevacizumab (1.5 mg). After 48 weeks, no statistically significant differences were found between the groups (16).

The Diabetic Retinopathy Clinical Research Network (DRCRN) study, conducted by Elman (17), compared the efficacy of Ranibizumab plus prompt laser (3 to 10 days after the injection) or deferred laser (after 24 weeks) with sham injections plus prompt laser or Triamcinolone (Trivaris) plus prompt laser. After 1 year, the groups who received Ranibizumab had better visual acuity compared to those treated with laser or Triamcinolone. After 2 years of follow-up the proportion of patients who gained more than 10 letters was not statistically different between the Ranibizumab plus prompt laser group compared to laser group, but there was a statistically significant difference between laser and Ranibizumab plus deferred laser. The authors of the study did not have an explanation for this fact.

Bevacizumab proved its efficacy in the treatment of diabetic macular edema in several prospective studies. The most well-known is Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT) study (18) which compared the intravitreal injections of Bevacizumab (1.25 mg) with laser photocoagulation. After 24 months of follow-up visual acuity was higher in the Bevacizumab group; also the proportion of patients who gained more than 10 letters was higher in the group treated with intravitreal injections.

Lam (19) compared 2 doses of Bevacizumab (1.25 mg versus 2.5 mg) for the treatment of diffuse diabetic macular edema. After 6 months, there was an improvement of visual acuity in both groups compared to baseline, but there was no difference between groups. The patients received 3 intravitreal injections during this period.

Four clinical trials investigated the combination of Triamcinolone and Bevacizumab.

Soheilian (20) compared 3 groups of patients with diabetic macular edema: the first group was treated with Bevacizumab, the second with laser photocoagulation, and the third with Bevacizumab plus Triamcinolone.

After 36 weeks, the visual acuity improved more in the bevacizumab group than the other two groups, although the difference was not statistically significant. After 24 months there were not statistically differences between the groups.

Intravitreal Bevacizumab with or without Triamcinolone for refractory diabetic maculat edema (ATEMD) study (21) included 3 groups of patients treated with Bevacizumab, Triamcinolone, and combined treatment, respectively. The outcomes were similar after 6 months.

Lim (22) studied the combination of Bevacizumab and Triamcinolone and compared it with Bevacizumab and Triamcinolone alone. No differences in best-corrected visual acuity or macular thickness between the groups were found after 12 months of follow-up.

Another study, conducted by Ahmadieh (23), compared 3 groups of patients with
diabetic macular edema who did not adequately respond to laser. Group I was treated with Bevacizumab (3 injections of 1.25 mg every 6 weeks) plus Triamcinolone (a single 2 mg injection), group II received Bevacizumab (administered in the same manner as in group I), and group III received sham injection. The visual acuity improved more in the first 2 groups compared to sham group, but there were not statistically differences between Bevacizumab group and the group on combined therapy.

*Pegaptanib* was studied only in two trials. Both studies compared this anti-VEGF agent with sham treatment.

Cunningham (24) conducted a study which compared 3 doses of Pegaptanib (0.3, 1 and 3 mg) with sham in patients who did not receive previous laser treatment. After 6 months, the first 2 groups had better functional outcomes than the 3 mg Pegaptanib or sham groups.

The second clinical trial, reported by Sultan (25) in 2011, compared the efficacy of Pegaptanib with sham. After 2 years of follow-up, visual acuity was significantly better in the treated group than in the sham group, but there was no difference in the proportion of patients who gained more than 10 letters.

*Aflibercept* is the newest anti-VEGF agent available and its efficacy in treating diabetic macular edema was proven by the Da Vinci trial (26). That study compared laser treatment with several doses of Aflibercept, and the functional outcomes were better for the anti-VEGF agent after 6 months. The best regimen proved to be 2 mg every 4 weeks.

The main complication after intravitreal injections is endophthalmitis. Because of the continuously increasing numbers of intravitreal injections that are performed worldwide, it has become the main cause of endophthalmitis.

**Corticosteroids**

*Dexamethasone* was studied in 2 important trials.

Haller (27) compared 2 doses of Dexamethasone (350 and 700 µg), administered as an intravitreal implant, with no treatment. After 3 months, only the patients who received 700 µg gained more than 10 letters in visual acuity. This difference was statistically significant (33% versus 12%). The 350 µg group showed a non-statistically significant improvement compared to laser.

After 6 months of follow-up there were no differences between the treated groups and the non-treated group. Dexamethasone had a maximum effect after 3 months, but the efficacy began to decline after that.

The second trial, by Callanan (28), included 2 groups of patients: one treated with laser, the other with laser plus Dexamethasone. Although in the first months better results were noticed in the Dexamethasone group, after 12 months of follow-up the authors did not find any differences between the groups.

*Fluocinolone* is another corticosteroid which was studied (as an intravitreal implant) for the treatment of diabetic macular edema. The *Fluoconolone Acetonide in Diabetic Macular Edema* (FAME) study (29) compared 2 doses of Fluocinolone (0.2 and 0.5 µg/day) with sham intravitreal injections in patients who had at least one laser treatment before being included in the study. After 24 months visual acuity was significantly better in the corticosteroid groups compared to sham. The differences between the 2 groups on Fluocinolone were
not significant.

Pearson (30) compared Fluocinolone with laser treatment. After 3 years, there was no difference between the groups regarding the proportion of patients who gained more than 15 letters in visual acuity.

Triamcinolone was evaluated in several comparative studies as intravitreal injections. The trials that included patients treated by laser and patients who received Triamcinolone showed better results for the laser groups (31). Ranibizumab was also superior to Triamcinolone, and the differences reached a statistical significance level.

The main complications of corticosteroids are cataract and glaucoma. Their incidence is directly dose-related. The biodegradable intraocular implants that release the corticosteroid in a controlled manner seems to have a better safety profile and an efficacy that is comparable to the anti-VEGF agents. In a recent study, published in Ophthalmology in February 2015, it is suggested that the first line of treatment should be the anti-VEGF agent for the phakic eyes and the biodegradable implant with Dexamethasone for the pseudophakic eyes.

CONCLUSIONS

In our opinion, the anti-VEGF agents proved their efficacy in treating diabetic macular edema. Ranibizumab was the most used agent in clinical trials. It is superior to laser, but the results of the different studies must be analyzed with moderation, because half of the patients will not have a driving vision.

Corticosteroids produced a more significant reduction in macular thickness compared to laser or anti-VEGF agents, but they were associated with secondary cataract and glaucoma.

Despite a wide spectrum of possibilities for treating diabetic macular edema, only a minority of patients achieve good vision (20/40), so future studies should bring new therapies for treating this condition.

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REFERENCES

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INFLAMMATORY HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. The incidence is increasing because of the increasing prevalence of chronic liver disease, both viral and metabolic. Uncommonly, HCC occurs in patients without cirrhosis. Lymphoepithelioma-like carcinoma (LELC) is defined as a tumor composed of large undifferentiated epithelial cells with a predominant lymphoplasmacytic component. These tumors are reported to occur in several organs, including nasopharynx, salivary glands, lungs and stomach and also have been uncommonly reported in trachea, lacrimal glands, ureters, urinary bladder, uterine cervix, vagina, ovaries, breast, soft tissue, and skin. Epstein-Barr virus (EBV) has been shown to be strongly associated with LELCs of the nasopharynx, stomach, salivary glands, lungs, and thymus in the form of integration of the viral genome in the tumor cell nuclei. However, this association has not been shown in LELCs of the urinary bladder, uterine cervix, or skin. Regardless of EBV status, the morphologic features and prognosis are the same, except for the uncommon sites where the prognostic information is limited. Human papilloma virus (HPV) DNA has been shown in the tumor cells of lymphoepitheliomas of the breast, and transcriptionally active HPV has been shown by in situ hybridization in LELCs of the oropharynx. There is controversial evidence of involvement of HPV in the uterine cervix; some authors report its presence, whereas others do not. The World Health Organization has recently recognized LELC, or inflammatory HCC (iHCC), as a variant of HCC. To date, LELCs of the liver have been reported in the form of cholangiocarcinoma (n = 20) and HCC (n = 9), with only 1 lymphoepithelioma-like HCC (LEL-HCC) being positive for EBV. The authors studied all cases of LELC of the liver of the institution from the past 23 years, by analyzing for the expression of p16 protein or the presence of HPV. They characterized the immunophenotype of the inflammatory cells within the tumors, the epithelial differentiation pattern of the tumor cells, features of the background liver, and the viral status of the tumor cells. All of the cases were HCC that arose in noncirrhotic livers, two showed biphenotypic differentiation, and none were positive for EBV or HPV (Patel KR, Liu TC, Vaccharajani N, et al. Characterization of Inflammatory Hepatocellular Carcinoma. Arch Pathol Lab Med. 2014;138:1193–1202).