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Diabetic macular edema management – international guidelines overview

Zarządzanie cukrzycowym obrzękiem plamki żółtej – przegląd międzynarodowych wytycznych

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Keywords

diabetic retinopathy, DR, diabetic macular Edema, DME, treatment options, management options, therapeutic options

Słowa kluczowe

retinopatia cukrzycowa, DR, cukrzycowy obrzęk plamki żółtej, DME, możliwości leczenia, opcje terapeutyczne

S u m m a r y

Diabetic Macular Edema (DME) is a severe disease, related to Diabetic Retinopathy (DR). All diabetic patients are at risk of DME development. The disease severity may vary from mild to moderate and severe, with risk of loss of vision. In the last years, DME management guidelines have been developed worldwide, and there is necessity to review these recommendations, to find the best therapeutic option for Diabetic Macular Edema Patients.

In this article authors summarize what are the current Diabetic Macular Edema management options based on the international and Polish clinical recommendations and guidelines.

The study and conclusions in this article are based on web-available data, officially published DME management guidelines of Royal College of Ophthalmologists (UK), Canadian Diabetes Association, American Association of Ophthalmologists, International Council of Ophthalmology and Polish Ophthalmology Society.

The guidelines have been thoroughly reviewed and summarized in this article. Guidelines of American Association of Ophthalmologists as well as International Council of Ophthalmology are the most advanced in detailed description of DME management and seems to represent the most comprehensive and advanced approach, based on the evidence-based medicine. Polish Ophthalmology Society panel of experts has developed its own guidance of Diabetic Macular Edema management. However the document is based on international studies and is aligned with mainstream international recommendations, it contains also a novel approach of anti-VEGF usage in DME management.

This study aimed to show what are the current Diabetic Macular Edema management options based on the clinical recommendations and guidelines. However no substantial differences have been identified amongst reviewed guidelines, but some specific to a guideline accents of what treatment alternative should be used and on what stage of DME are visible. These diversities should be considered by ophthalmologists always when looking for the targeted therapeutic option to a specific DME patient.

S t r e s z c z e n i e

Cukrzycowy obrzęk plamki żółtej (DME) jest ciężką chorobą, związaną z retinopatią cukrzycową (DR). Wszyscy pacjenci z cukrzycą są narażeni na ryzyko rozwoju DME. Nasilenie choroby może wahać się od stanu łagodnego do umiarkowanego i ciężkiego, z ryzykiem utraty wzroku. W ostatnich latach na całym świecie zostały opracowane wytyczne dotyczące zarządzania DME, w związku z czym istnieje konieczność dokonania przeglądu tych zaleceń, by móc znaleźć najlepszą opcję terapeutyczną dla pacjentów z cukrzycowym obrzękiem plamki żółtej.W niniejszym artykule autorzy, opierając się na międzynarodowych i polskich zaleceniach klinicznych, podsumowują obecne kierunki leczenia cukrzycowego obrzęku plamki żółtej. Badania i wnioski w tym artykule są oparte na oficjalnie dostępnych danych internetowych, opublikowanych wytycznych leczenia DME takich organizacji jak: Royal College of Ophthalmologists (Wielka Brytania), Canadian Diabetes Association (Kanada), American Association of Ophthalmologists (USA), International Council of Ophthalmology (USA) i Polskiego Towarzystwa Okulistycznego. Omawiane w artykule rekomendacje zostały dokładnie przeanalizowane i podsumowane. Wytyczne American Association of Ophthalmologists i International Council of Ophthalmology są najbardziej wyczerpujące pod kątem zapisów, jak należy zarządzać DME. Wydaje się, iż stanowią one najbardziej kompleksowe i zaawansowane podejście, które opiera się na medycynie opartej na faktach (Evidence Based Medicine). Panel ekspertów Polskiego Towarzystwa Okulistycznego opracował własne wytyczne zarządzania cukrzycowym obrzękiem plamki żółtej. Dokument ten jest oparty na badaniach międzynarodowych i jest zgodny z głównym nurtem międzynarodowych zaleceń leczenia DME. Zawiera on również stosunkowo innowacyjne podejście w stosowaniu preparatów anty-VEGF w leczeniu DME.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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Celem tego artykułu było podsumowanie obecnych opcji zarządzania cukrzycowym obrzękiem plamki żółtej na podstawie uznanych międzynarodowych rekomendacji. Choć wśród analizowanych treści nie zidentyfikowano istotnych różnic w zarządzaniu DME, to niektóre akcenty różnicujące typu jaki typ leczenia należy zastosować i kiedy, są widoczne. Taka różnorodność w podejściu powinna być zawsze rozpatrywana przez okulistów przy poszukiwaniu najlepszej opcji terapeutycznej dla konkretnego pacjenta z DME.

INTRODUCTION

Diabetic Macular Edema (DME) is a severe disease, related to the Diabetic Retinopathy (DR). All diabetic patients are at risk of DME development. The disease severity may vary from mild to moderate, with risk of loss of vision. 25-30% non-ophthalmology treated, and up to 15% ophthalmology treated diabetic patients might be affected by moderate loss of vision due to DME (1). Based on the Rohit Varma, Neil M. Dressler study published in JAMA Ophthalmology weighted DME prevalence in USA is 3.8% (2.7-4.9%) of diabetes (2), however the meta-analysis of 35 studies (22,896 patients from United States, Australia, Europe and Asia) calculates DME prevalence on 7.48% (7.39-7.57) of the overall diabetes population (3).

Progression to DME affects 3% of mild non-proliferative DR eyes, 38% moderate and severe non-proliferative DR eyes and relates up to 71% eyes of the proliferative Diabetic Retinopathy – the most vision-threatening form of the disease (4, 5).

According to the Los Angeles Latino Eye Study and in the Proyecto VER study – 18% of participants with diabetes of more than 15 years' duration had the proliferative DR, with no PDR percentage difference between type 1 vs type 2 diabetes (6, 7).

Polish National Health Fund (NFZ) estimates diabetes patients on 2 million in Poland (8). Based on NFZ data and referring to cited above Rohit Varma as well as Yau et al. studies, authors calculate DME prevalence from 76.000 to 149.000 patients in Poland (2, 3).

On the authority of Wilkinson et al. Diabetic Macular Edema is classified to mild – where some retinal thickening or hard exudates in posterior pole but outlying from the center of the macula, moderate where retinal thickening or hard exudates approaching the center of the macula but not involving the center and severe, where retinal thickening or hard exudates involving the center of the macula (9).

Based on selected international and Polish guidelines published in years 2012-2016 authors analyze what are the clinical recommendations in vision loss prevention amongst Diabetic Macular Edema patients, what are the current treatment options and what are the perspectives for the future.

The study and conclusions in this article are based on web-available data, officially published DME management guidelines of Royal College of Ophthalmologists (RCO, UK) – publication in year 2012, Canadian Diabetes Association (CDA, CAN) – publication in year 2013, Polish Ophthalmology Society (POS, PL) – publication in year 2014, American Association of Ophthalmologists (AAO, US) – last publication in year 2016 and International Council of Ophthalmology – first publication in year 2013, the latest publication in year 2016 (ICO, US).

The guidelines have been methodically read and key DME management tactics: screening of the patients, the disease assessment and treatment introduction have been summarized and compared one to another.

DISCUSSION

In December 2012 the Royal College of Ophthalmologists, United Kingdom, published 'Diabetic Retinopathy Guidelines' (10) where Diabetic Retinopathy, including Diabetic Macular Edema management is precisely described.

Risk factors such as non-modifiable: genetic components, gender and duration of mellitus patients and modifiable: glycemia, blood pressure and lipid levels are considered as those which are playing main role for DR and DME development. Also carotid arterial disease, pregnancy, renal impairment and smoking should be taken into account in the complex disease management process (10).

According to the RCO recommendations, maintaining proper parameters of modifiable DR risk factors through effective treatment of primary diseases, have significant positive impact on long-term outcome of retinopathy. In the paper these have received 'Level 1' evidence (which is based on results of randomized controlled trials – RCTs) and mostly 'Level A' recommendations (where strength of evidence was universally agreed) (10).

Irrespectively of DR risk factors management strategies, RCO identifies four main therapeutic options of the DME treatment. These are laser photocoagulation, intravitreal steroid treatment, intravitreal VEGF inhibitors and polytherapy of laser photocoagulation + VEGF or + intravitreal steroid treatment (10).

RCO also considers vitrectomy for removal of hard exudates and for non-ischaemic diffuse DME when grid laser treatment does not bring expected results, but the evidence is based on case studies (10).

In year 2013 the Canadian Diabetes Association issued clinical practice guidelines (11) where experts committee emphasizes the necessity of mellitus patients screening, type 1 diabetes, all individuals $\geq$ 15 age, 5 years after diagnosis, and in all type 2 diabetes at diagnosis. If retinopathy is detected, then sight-threatening DR treatment should be introduced. Monitoring of the disease progress to be continued at least once per year. If DR is not present, then re-screening rhythm should be assigned, annually in all type 1 diabetes and type 2 diabetes every 1-2 years (11).

Despite direct DR treatment, CDA also recommends proper control of glycaemia, blood pressure and lipids to 'reach targets per guidelines', as these impact factors play an important role of retinopathy development. However anti-platelet therapy with ASA seems to be not associated with DR progression (11).

American Association of Ophthalmologists (AAO) published in year 2016 an updated preferred practice pattern (PPP) guidelines of Diabetic Retinopathy management (12).

AAO PPP guidelines are reviewed by panel of experts on an annual basis, and either no commercial financial support to these guidelines nor authors or reviewers received financial compensation for their work on the paper (12).

Key findings highlighted by AAO refer to necessity of type 1 and type 2 diabetes screening for DR and continuous controlling of glucose, blood pressure and serum lipids as abnormal levels of these parameters have significant impact on DR progression. All diagnosed non-proliferative, proliferative DR and diabetic macular edema patients must be referred to ophthalmologists. Concomitantly to CDA guidelines, AAO recommends follow up of DME progression at annual basis, irrespectively to type of mellitus (12).

As specified in the AAO guidelines, DR and DME diagnosis physical examination include primary disease history assessment like duration of diabetes, glycaemia and lipids levels, systemic hypertension, renal disease, obesity, ocular history and medicaments taken. Ocular examination should comprise from visual acuity assessment, intraocular pressure, pupillary assessment, funduscopy including examination of the posterior pole and examination of the peripheral retina and vitreous (12). Additional tests like color and red-free fundus photography, optical coherence tomography, fluorescein angiography and ultrasonography might enhance physical examination, and treatment outcomes follow up (12).

In year 2013 the International Council of Ophthalmology (ICO) released first time guidelines for Diabetic Eye Care. The ICO diabetic eye care committee consists from international experts of ophthalmology from the North and South Americas, Asia, Australia and Europe. The guidelines are updated on a regular basis and the newest release is elaborated for year 2017 (13). The ICO classifies diabetic eyes as having no Diabetic Macular Edema, non-central involved DME and central-involved DME (tab. 1) (13).

Tab. 1. Classification of Diabetic Macular Edema according to ICO (13)

Diabetic Macular Edema	Observations on dilated ophthalmoscopy
No DME	No retinal thickening or hard exudates in the macula
Noncentral--involved DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1 mm in diameter
Central-involved DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter

An excellent tool for grading Diabetic Retinopathy including Diabetic Macular Edema is available online at www.drgrading.iehu.unimelb.edu.au.

For non-central involved DME, ICO experts recommend the disease progress assessment every 3 months, for central involved DME every 1 month (tab. 2).

Tab. 2. DME progress assessment according to ICO (13)

Classification of DME	Next screening schedule	Referral to Ophthalmologist
Noncentral-involved DME	3 months	required
Central-involved DME	1 month	required

According to ICO guidelines, proper DR and DME management includes screening of the patients, detailed ophthalmic assessment and treatment of DME (fig. 1) (13).

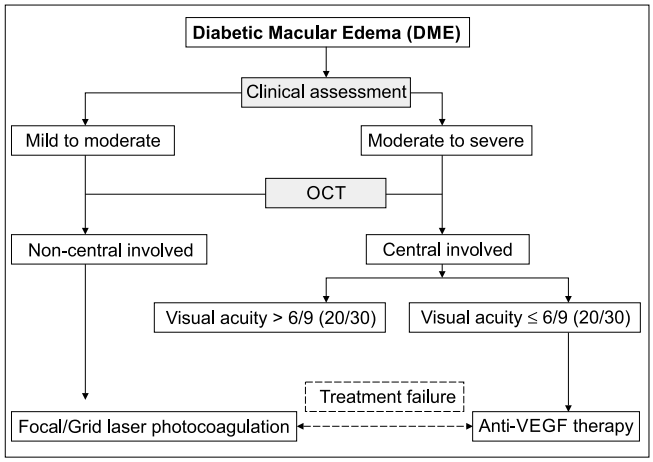

Fig. 1. DME treatment decision tree as per ICO (13)

Screening of the patients comprises of complete ophthalmic examination, including an identification of DR. While the detailed ophthalmic assessment covers (13):

- patient medical history with key elements like duration of mellitus, glycemia and ocular history, medicaments taken and other systemic diseases presence,
- physical exam through visual acuity assessment, measurement of intraocular pressure, gonioscopy when indicated, slit-lamp biomicroscopy and fundus examination,
- follow up examination comprising of follow up history, follow up physical exam, ancillary tests (optic coherence tomography – OCT, fundus photography, fluorescein angiography) and patients education.

ICO guidelines pay special attention to OCT, describing this method as the most sensitive in DME identification, that allows quantitative disease assessment (13).

Laser photocoagulation in DME treatment is used since 80s'. The Early Treatment Diabetic Retinopathy Study (ETDRS) and its treatment focal/grid protocol is the most preferable by RCO as has the most clinical evidence (Level 1) with proven clinically vision loss reduction (10). Alternatively, the photocoagulation in DME treatment can be performed with the sub-threshold micropulse laser (vs ETDRS procedure with supra-threshold laser). Potentially sub-threshold laser (Level 2) can be considered as less aggressive vs standard photocoagulation. In comparative study on 50 patients, no significant difference in visual acuity and central retinal thickness has been observed, but central retinal sensitivity improved and fundus autofluorescence was preserved when micropulse laser has been used. As per RSO more clinical experience needs

to be gathered in this type of laser to recommend it over ETDRS protocol (10). CDA guidelines also confirm laser photocoagulation benefits in DR and DME treatment. According to the studies referred by Canadian experts, laser treatment reduces loss of vision by 90% in severe DR proliferative on non-proliferative retinopathy and by 50% the incidence of visual loss in clinically significant macular edema (CSDME) (11).

As per AAO guidelines laser photocoagulation is a traditional treatment for clinically significant macular edema, and many of clinicians still prefer to use modified ETDRS treatment, and in spite of new era of VEGF inhibitors (12), laser photocoagulation persists preferred treatment for non-center-involving macular edema (12). Advantages of this therapeutical option resulting from greater spacing, direct targeting of micro-aneurysms, and avoiding foveal vasculature within at least 500 μm of the center of the macula (12). When deciding for the laser photocoagulation in DME treatment, ophthalmologists need to consider rare but severe adverse side effects of the focal type laser photocoagulation that might induce sub-retinal fibrosis with choroidal neo-vascularization, a complication that may be associated with permanent central vision loss. Patients with high levels of sub-retinal hard exudates and increased serum lipids might be at higher risk of sub-retinal fibrosis development after the photocoagulation (12). Also AAO experts rise the risk of DME exacerbation with increased risk of moderate vision loss in panretinal photocoagulation which is widely used in induction of regression of retinal neo-vascularization (12).

ICO guidelines consider laser photocoagulation for both non-central involved and central involved DME. For non-central involved DME focal laser is advised to leaking microaneurysms, if thickening is threatening the fovea'. No treatment is recommended to lesions closer than 300-500 μm from the center of the macula (13). For central involved Diabetic Macular Edema, ICO proposes laser photocoagulation as therapeutical option for eyes with good or without good visual acuity, but always as secondary choice, especially in eyes with persistent retinal thickening despite anti-VEGF treatment, when anti-VEGF treatment is not available or monthly follow up is not possible (13).

Intravitreal steroids are less recommended for the DME management and should be used in case of unresponsiveness to other treatment options. Intravitreal preservative-free triamcinolone, intravitreal dexamethasone and sustained release intravitreal fluocinolone implant have been investigated in various, randomised trials. Undertaken studies demonstrated mainly short and medium term benefits of the intravitreal steroids in DME treatment. Especially long acting fluocinolone is effective (level 1) in DME treatment, and can be considered as alternative to VEGF inhibitors, i.a. thanks to reduced frequency of the course of medication, but all types of intravitreal steroids demonstrated relatively high risk of side-effects, like intraocular pressure, glaucoma and cataract. All of these have to be taken into account and balance the overall benefits of steroids usage in DME management (10). CDA panel of experts, describe intravitreal steroids as an alternative option to VEGF inhibitors, but the same as RCO emphasises increased risk of glaucoma and cataract when intravitreal steroids are used in DR.

AAO guidelines shortly describe use of eye steroids in diabetic macular edema management. However based on the several studies short- and long-term intravitreal steroids show benefits in an early decrease in retinal thickness and visual acuity gain in pseudophakic eyes when treated with laser, but as per AAO anti-VEGFs tend to be better overall in DME management and therefore intravitreal steroids efficacy and safety profile need to be investigated subsequently (12).

ICO guidelines consider intravitreal triamcinolone mainly in central-involved DME, pseudophakic eyes (13).

Intravitreal VEGF inhibitors play very important role in DME management, as vascular endothelial growth factor stimulates vasculogenesis and angiogenesis, also increases vessel permeability. Over-expression of VEGF can cause retina diseases, such as DR (14).

The first anti VEGF treatment in DME was Pegaptanib showing significant improvement on visual acuity and retinal thickness vs control group, but only Ranibizumab achieved level 1 evidence proved by the studies READ-2, RESOLVE, RESTORE and RIDE. Ranibizumab achieves superior results of vision improvement of DME patients (10).

Bevacizumab is not formally registered in DME treatment, as it is used mainly in AMD, but several studies, like BOLT and MACORES show Bevacizumab efficacy in diabetic macular edema (10). Comparing to Ranibizumab and Bavicizumab, Afilbercept is discerned as with higher binding affinity, so potentially has a longer time of activity (15), that can improve rhythm of injections. In DAVINCI study Afilbercept confirmed its efficacy in DME, improving visual acuity from 9.7 letters up to 13.1 letters after one year of treatment (10). CDA guidelines allude to the same studies as RCO, confirming high efficacy of VEGF inhibitors in DME treatment (11).

AAO guidelines recognize intravitreal injections of VEGF inhibitors as effective treatment and based on the many studies showing visual acuity improvement in DME patients, these should be considered as first choice therapy for center-involving DME (12). Pre-treatment or contaminant use of eye antibiotics during anti-VEGF therapy is not recommended, but betadine antiseptic drops and a lid speculum are suggested to complete the intravitreal treatment (12). As in other DME treatment options, physicians must take into account adverse side effects that might appear during intravascular injections combining from infectious endophthalmitis, cataract formation and retinal detachment (12). ICO guidelines recommend anti-VEGFs as de facto primary therapeutic option for central-involved DME. According to ICO, all available VEGF inhibitors used in DR, like ranibizumab, bevacizumab and aflibercept exhibit high therapeutic effect in DME treatment with good safety profile (13). No significant, long term differences in treatment efficacy is observed amongst available anti-VEGFs (13). DME patients receiving anti-VEGF treatment should be monitored with optical coherence tomography

on a monthly basis in the first, second and up to 5th year of injections, however in the first year of treatment 8-10 injections are considered, in the second year 2-3 injections, in the third year 1-2 injections and in the fourth and fifth year of treatment 0-1 injections (fig. 2) (13).

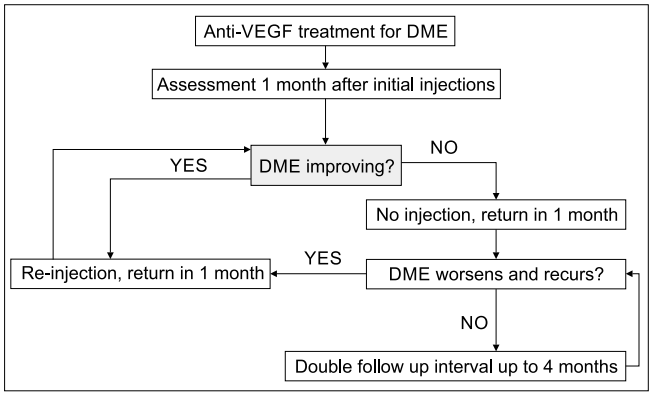

Fig. 2. Anti-VEGF treatment decision tree as per ICO and DRCR.net study (13)

Combination therapies of VEGF inhibitors with photocoagulation achieves questionable results versus VEGF inhibitors alone, but significantly better results versus laser therapy alone. The combination therapy of VEGF inhibitors and photocoagulation comparing to VEGF inhibitors alone theoretically should convey incremental benefits of the DME management, but in the RESTORE study, where one of the control groups received both types of treatment did not prove this assumption. There were no statistical difference in visual impairment improvement versus VEGF inhibitor used in monotherapy (10).

As per ICO guidelines for eyes with persistent retinal thickening complementary treatment of laser photocoagulation is considered (10).

Simultaneously, no synergistic benefit is observed in polytherapy of intravitreal steroids and photocoagulation versus intravitreal steroids or laser therapy alone. But there is level 1 evidence that intravitreal steroids combined with photocoagulation treatment is inferior to VEGF inhibitors with immediate or deferred laser, except in patients who are pseudophakic (10).

SURGICAL INTERVENTION

CDA panel of experts widely comments eye surgical intervention – vitrectomy – as treatment option for severe vitreous hemorrhage and severe proliferative diabetic retinopathy, including diffuse macular edema with or without vitreomacular traction. According to Diabetic Retinopathy Vitrectomy study (17), the surgical treatment option in these patients might bring incremental therapy benefits in severe mellitus vision impairment patients (11).

American Academy of Ophthalmology experts consider pars plana vitrectomy in clinically significant macular edema patients to achieve visual acuity improvement when substantial vitreomacular traction is present, but this therapeutical option should be used in case of limited or no improvement after photocoagulation and/or VEGF intravitreal inhibitors usage (12).

International Council of Ophthalmology guidelines identify precisely five indications for vitrectomy in DME (13):

1. Severe vitreous hemorrhage of minimum 1-3 months duration that does not disappear automatically.
2. Advanced active proliferative DR that persists despite extensive pan retinal photocoagulation.
3. Recent traction macular detachment.
4. Combined traction-rhegmatogenous retinal detachment.
5. Tractional macular edema or epiretinal membrane involving the macula.

POLISH VS INTERNATIONAL GUIDELINES OF DME MANAGEMENT

In year 2014, Polish Ophthalmology Society revealed its own document of Diabetic Macular Edema management. All guidance is based on international studies and are aligned with international recommendations, emphasizing necessity of proper mellitus care, at is it proven that intense dyslipidemia control, blood pressure and glucose levels decrease risk of CSDME development. Also full metabolic control results in retina thickness reduction and visual acuity improvement in mild DME patients (18). Polish Ophthalmology Society highlights efficacy of laser photocoagulation and anti-VEGFs in DME treatment options (18). Intravitreal steroids are less recommended due to potential severe side effects like glaucoma and cataract (18). In Poland only ranibizumab (Lucentis, Novartis) and aflibercept (Eylea, Bayer) are registered for DME treatment (18, 19). Other VEGF inhibitor bevacizumab (Avastin, Roche) or intravitreal steroids like triamcynolon (Kenalog, E.R. Squib) or fluocynolon (Iluvien, Alimera) are used in DME as off-label treatment options (18).

What is novel comparing to the international guidelines, Polish Ophthalmology Society panel of experts has developed three different assessment levels of anti-VEGF usage in DME management (18):

1. Exclusion criteria for anti-VEGF treatment:
   - macular morphological state functional improvement is not expected,
   - visual acuity improvement < 0.05.
2. Criteria to confirm treatment success:
   - visual acuity ≥ 1.0 or,
   - no fovea edema confirmed via optical coherence tomography or fluorescein angiography.
3. Criteria for treatment effectiveness:
   - vision improvement of at least one line in the last 3 months,
   - confirmed in OCT reduction of edema in central retina by 10% in the last 3 months.

Comparably to ICO guidelines, Polish Society of Ophthalmology recommends surgical intervention (vitrectomy) in case of tractional macular edema or epiretinal membrane involving the macula (18).

In Poland DME treatment is within Diagnosis Related Groups (JGP system) as of B16, B17, B83, B84 and B98. However the valuation of a group, consisting from ICD-9 procedures is not directly linked with DME management, and it generates economical treatment

barriers as it was widely described in the article, Diabetic Macular Edema treatment limits in Poland' (20).

CONCLUSIONS

This study aimed to show what are the what are the current Diabetic Macular Edema management options based on the clinical recommendations and guidelines. However no substantial differences have been identified amongst reviewed guidelines, but some specific to a guideline accents of what treatment alternative should be used and on what stage of DME are visible. These diversities should be considered by ophthalmologists always when looking for the targeted therapeutic option for a specific DME patient. Guidelines of American Association of Ophthalmologists and International Council of Ophthalmology are the most advanced in detailed description of DME management and seems to represent the most comprehensive and advanced approach, based on the evidence based medicine. Although none of the guidelines directly identified a 'gold standard' of DME treatment, but based on the medical studies referred by panel of experts, VEGF inhibitors manifest themselves as those with highest efficacy in vision loss prevention amongst DME patients, irrespectively of central or non-central involved DME. Laser photocoagulation, in spite of highest experience gathered for the last thirty years of clinical practice, gradually giving way to more efficient anti-VEGFs, especially in central involved DME.

Intravitreal steroids have limited recommendations in DME treatment (mainly to pseudophakic eyes), due to possible severe side effects like cataract, glaucoma or IOP that might appear in DME management. Vitrectomy is recommended in a very specific DME related indications, when macular detachment or vitreous hemorrhages is observed independently of typical DME symptoms.

Combination therapy of anti-VEGFs and laser photocoagulation versus VEGF inhibitors or laser photocoagulation alone might give incremental benefits in DME management, however in long term perspective this must be confirmed further in clinical experience and medical studies.

All DME management guidelines pay special attention to DME development risk factors like glycemia, blood pressure and dyslipidemia, that are considered as those which are playing main role for DR and DME development. Also patients education and treatment compliance play and important role in the disease prognosis.

Bearing in mind all above considerations, it is important to maximize access of DME patients to the most advanced therapeutic options in order to minimize risks of vision loss and long term consequences of inefficient DME management.

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received/otrzymano: 08.02.2017
accepted/zaakceptowano: 28.02.2017