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Custom-Designed Approach to Treatment with Algorithms (C-DATA) for Diabetic Macular Edema

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Keywords

Diabetic Macular Edema; Custom-Designed Treatment Algorithm (C-DATA); Anti-VEGF Therapy; Intravitreal Injections; Personalized Medicine

Abstract

Objective: To evaluate the efficacy of a custom-designed approach to treatment with algorithms (C-DATA) for diabetic macular edema (DME) compared to established published protocols.

Design: Prospective, comparative clinical study.

Subjects: 33 patients with DME, contributing to 49 distinct eyes treated.

Methods: Patients were treated according to the C-DATA algorithm, which guided the selection and timing of intravitreal injections, subtenon injections, and focal grid laser therapy based on individual patient characteristics and treatment responses. Comprehensive ophthalmic examinations, including Optical Coherence Tomography (OCT), were performed at each visit.

Main Outcome Measures: Best-corrected visual acuity, treatment frequency, and patient dropout rate.

Results: Eyes treated with C-DATA showed a mean improvement of 14.7 letters over an average follow-up period of 37.2 months, compared to 8.2 letters for eyes treated with standard protocols. 71.4% of C-DATA-treated eyes improved, gaining an average of 22.14 letters. C-DATA required an average of 2.6 treatments per year, compared to 10.6 treatments per year for regimented protocols. The dropout rate for C-DATA was 1.9%, versus 11.4% for standard protocols.

Conclusions: The C-DATA approach for DME management demonstrated superior visual acuity outcomes, significantly reduced treatment burden, and enhanced patient compliance compared to traditional regimented protocols. These findings suggest that personalized, algorithm-based treatment strategies may optimize DME management and improve long-term patient outcomes.

Introduction

Diabetic macular edema (DME) is a common and potentially sight-threatening complication of diabetic retinopathy that occurs when fluid accumulates in the macula. If left untreated, DME can lead to significant and sometimes irreversible reduction in visual acuity, severely impacting a patient's quality of life. The management of DME has evolved significantly over the past few decades. In 1985, the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) evaluated the role of focal grid laser therapy for clinically significant DME and established it as the standard of care at the time. This approach remained the primary treatment option for many years, providing a foundation for DME management.[1]

However, the landscape of DME treatment changed dramatically with the advent of anti-vascular endothelial growth factor (anti-VEGF) therapies. These treatments, administered as intravitreal (IV) injections, have revolutionized the management of DME.[2] In addition to anti-VEGF agents, steroids have emerged as another valuable therapeutic option. Administered either as intravitreal or subtenon injections, steroids are particularly beneficial in cases of anti-VEGF resistance and chronic DME. This multi-modal approach to DME management and variable dosing regimens allow clinicians to tailor treatment to individual patients' needs and responses.[3]

Traditionally, the administration of intravitreal injections and laser treatments has been guided by protocols derived from major multicenter clinical trials and/or subsequent modifications of these protocols. While these standardized approaches have been valuable, especially for clinical trials, they may not always account for the heterogeneity of DME presentation and individual patient responses to treatment. Notably, custom-designed, response-based algorithms have not been previously developed, tested, or implemented on a wide scale in DME management.

Given the variability in DME presentation and treatment response, there is a clear need for more personalized treatment strategies. This study aims to address this gap by developing and evaluating a custom-designed approach to treatment with algorithms (C-DATA) for DME. Our primary objective is to determine whether this tailored approach can provide a more effective guide for treating patients with DME compared to established published protocols. By doing so, we hope to contribute to the ongoing effort to optimize DME management and improve outcomes for patients affected by this challenging condition.

Methods

This prospective study evaluated the efficacy of a custom-designed approach to treatment with algorithms (C-DATA) for DME. All comers presenting with DME were treated based on the C-DATA protocol. To ensure adequate follow-up and data collection, only patients with a minimum of 8 continuous months of care and follow-up were included in the final analysis. Study participation

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was terminated when an intra-ocular procedure was performed, if a significant ocular event occurred, or if a patient was lost to follow-up.

A total of 49 eyes from 33 patients met the above inclusion criteria.Comprehensive ophthalmic examinations were performed at each visit. These included Optical Coherence Tomography (OCT) to assess retinal thickness and morphology, best-corrected visual acuity measurement, intraocular pressure (IOP) measurement and anterior segment examination.Vitreous and dilated retinal examinations as well and fluorescein angiography (FA) were conducted when clinically indicated.

Patients were treated according to the C-DATA algorithm (Figure 1). This algorithm guided the selection and timing of various treatment modalities based on individual patient characteristics and treatment responses. The available treatment options included intravitreal (IV) injections of Bevacizumab (Avastin), Ranibizumab (Lucentis), Aflibercept (Eylea), or Dexamethasone implant (Ozurdex); subtenon (ST) injections of Dexamethasone or Triamcinolone; and focal grid laser therapy. The C-DATA algorithm provided a structured yet flexible approach to treatment selection, allowing for personalized care based on each patient's clinical presentation and response to previous interventions.

Throughout the study, detailed records were maintained for each patient, including OCT measurements, visual acuity scores, treatment decisions, and any adverse events. These data were systematically collected and analyzed to evaluate the efficacy of the C-DATA approach compared to traditional treatment protocols. Statistical analysis was performed using the `scipy.stats` module from the SciPy library in Python 3. Comparison between pretreatment Best Corrected Visual Acuity (BCVA) and posttreatment BCVA at the end of follow-up period was performed using the paired t-test. A p-value <0.05 was considered statistically significant. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the West Virginia University Eye Institute. Informed consent was obtained from all participants prior to their inclusion in the study.

Results

The study findings demonstrated a significant improvement in visual acuity for eyes treated using the custom-designed approach to treatment with algorithms (C-DATA) compared to those treated with regimented protocols [4–12]. A total of 49 eyes from 33 patients were included in the study. The mean age of participants was 66.1 ± 10.7 years, with a fairly even sex distribution of 16 males (48%) and 17 females (52%) (Table 1). Eyes managed with C-DATA exhibited a mean improvement of 14.7 letters over an average follow-up period of 37.2 months (p<0.001). In contrast, eyes treated according to standard regimented protocols showed a lesser improvement of 8.2 letters over the same mean follow-up period of 37.2 months. These results are summarized in (Table 2) and visually represented in (Figure 3). A more detailed analysis of the C-DATA treatment outcomes revealed that a substantial majority of treated eyes experienced visual improvement and/or stabilization. Specifically, 71.4% of eyes managed with C-DATA showed enhanced vision, with an average gain of 22.14 letters. A small proportion of eyes, 12.2%, experienced a decline in vision, losing an average of 9.37 letters. The remaining 16.3% of eyes maintained stable vision throughout the follow-up period. These outcomes are presented in (Table 4) and illustrated in (Figure 5). The C-DATA approach also demonstrated efficiency in terms of treatment frequency. Eyes managed using this algorithm received an average of 2.6 treatments per year. This annual treatment regimen typically consisted of 1.89 intravitreal injections, 0.36 subtenon injections, and 0.39 laser treatments. Notably, the dropout rate for patients treated with C-DATA was remarkably low at 1.9%. These statistics are detailed in (Table 3) and graphically represented in (Figure 4). In stark contrast, eyes treated according to regimented protocols required a significantly higher number of interventions, averaging 10.6 treatments per year. This increased treatment burden was associated with a substantially higher dropout rate of 11.4% for patients following standard protocols. The comparative treatment frequencies and dropout rates between C-DATA and regimented protocols are illustrated in (Figure 4).

Table 1: Baseline demographic characteristics, means ± SD or N (%)

Characteristics	
Number of patients	33
Number of eyes	49
Mean age ± SD (†yrs)	66.1 ± 10.7
Sex, N (%)	
Male	16 (48)
Female	17 (52)
Mean follow-up ± SD (††mos)	37.2 ± 25.8

Table 2: Study characteristics of the trials considered as other studies

Study ID	Follow-up (mos)†	Number of treatments/yr††	Average number of letters changed
Berger et al. (2015) [1]	12	12	5.8
Gillies et al. (2014) [2]	12	11.3	7.3
Nepomuceno et al. (2013) [3] Wells et al. (2015) [4]	11 12	9.6 10	13 11.4
Arevalo et al. (2013) [5]	24	4	7.7
Berger et al. (2013) [6]	12	12	5.8
READ-3 (2016) [7]	6	12	9.4
RESOLVE (2010) [8]	12	11.7	7.8
RESTORE (2011) [9]	12	10	6
REVEAL (2015) [10]	12	10.5	5.8
RISE (2012) [11]	24	13	9.2
RIDE (2012) [11]	24	13	9.6
BOLT (2010) [12]	12	9	8
Mean	**14.2**	**10.6**	**8.2**

†mos: months, ††yrs: years

Table 3: Average Number of Treatments Per Year

Type	
Intravitreal injections	1.89
Subtenon injections	0.36
Laser	0.39
Total	**2.64**

Table 4: Average Number of Letters Changed in the C-Data group

Change	
Improved	22.14
Worsened	9.37

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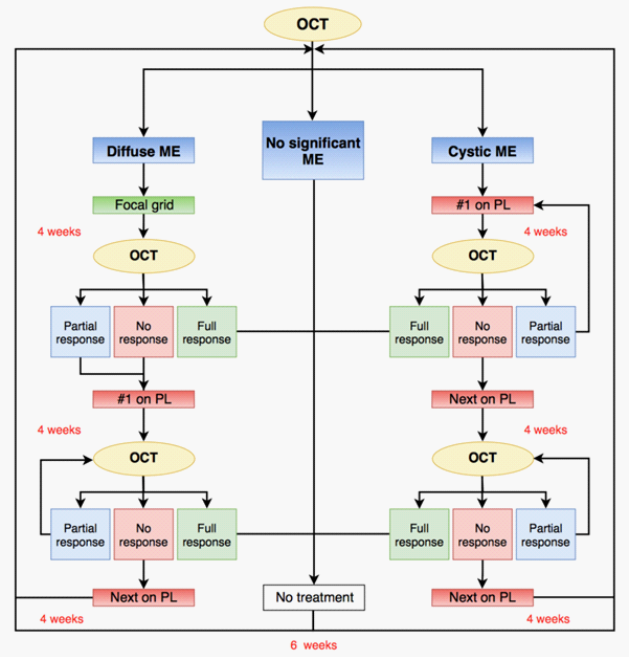

Figure 1: C-DATA Algorithm (PL= Preference List)

Discussion

The findings of this study demonstrate the potential benefits of a custom-designed approach to treatment with algorithms (C-DATA) for DME compared to traditional regimented protocols. The results suggest that C-DATA offers improved visual outcomes, reduced treatment burden, and enhanced patient compliance.

A notable finding of this study is the improvement in visual acuity achieved with C-DATA. Eyes treated using this approach showed a mean improvement of 14.7 letters over an average follow-up period of 37.2 months, compared to 8.2 letters for eyes treated with standard protocols. This difference of 6.5 letters is significant, potentially translating to meaningful improvements in patients' daily visual function and quality of life. Furthermore, the detailed analysis of C-DATA outcomes reveals that a substantial majority (71.4%) of treated eyes experienced visual improvement, with an impressive average gain of 22.14 letters. This suggests that the personalized approach of C-DATA may be more effective in addressing the heterogeneous nature of DME and individual patient responses to treatment [13]. An important benefit of C-DATA appears to be its efficiency in terms of treatment frequency.The average of 2.6 treatments per year under C-DATA stands in stark contrast to the 10.6 treatments per year required by regimented protocols. This fourfold reduction in treatment burden has significant implications for both patients and healthcare systems. Fewer treatments mean less disruption to patients' lives, reduced risk of injection-related complications, and potentially lower anxiety associated with frequent medical procedures. The substantial reduction in treatment frequency could also lead to significant cost savings and more efficient use of healthcare resources. Perhaps most notably, the dramatically lower dropout rate observed with C-DATA (1.9% vs. 11.4% for regimented protocols) suggests that patients find this approach more manageable

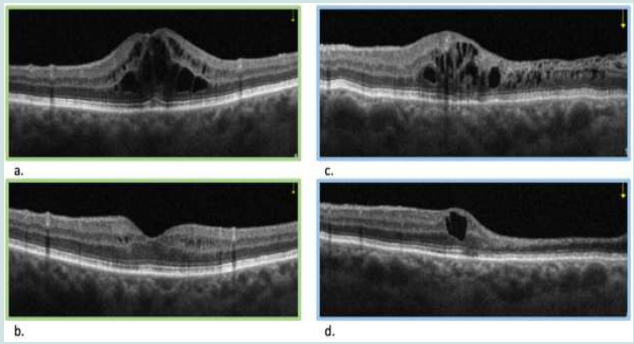

Figure 2: Optical coherence tomography (OCT) of a typical patient with full response [Figure 2a. (top left) and 2b. (bottom left)] and a typical patient with a partial response to treatment [Figure 3a. (top right) and 3d (bottom right].

Baseline OCT Assessment

- Perform baseline optical coherence tomography (OCT) on all eyes.
- Classify into three categories: diffuse macular edema (ME), no significant ME, or cystic ME

Treatment Protocol Based on Baseline OCT

A. DME

a. Perform focal grid laser

b. Conduct follow-up OCT after 4 weeks

c. Assess response:

i. Full response: No additional treatment, reassess with OCT after 6 weeks

ii. Partial or no response: Proceed to first treatment on preference list, reassess with OCT after 4 weeks

B. No Significant ME

a. No treatment given

b. Reassess with OCT after 6 weeks

C. Cystic ME

a. Administer first treatment on preference list

b. Conduct follow-up OCT after 4 weeks

Follow-up Protocol

A. Second OCT (4 weeks after initial treatment)

a. Full response: No additional treatment, reassess with OCT after 6 weeks

b. Partial response:

i. For diffuse ME: Administer first treatment on preference list

ii. For cystic ME: Repeat first treatment on preference list

c. No response: Administer next treatment on preference list

d. Reassess with OCT after 4 weeks in all cases of partial or no response

B. Third OCT (4 weeks after second treatment, if applicable)

a. Full response: No additional treatment, reassess with OCT after 6 weeks

b. Partial response: Readminister same treatment, reassess with OCT after 4 weeks

c. No response: Administer next treatment on preference list, reassess with OCT after 4 weeks

Response Definitions: Full response: complete resolution of ME see (Figure 2a) (Figure 2b). Partial response: incomplete resolution of ME see (Figure 2c) (Figure 2d). No response: no significant change in ME

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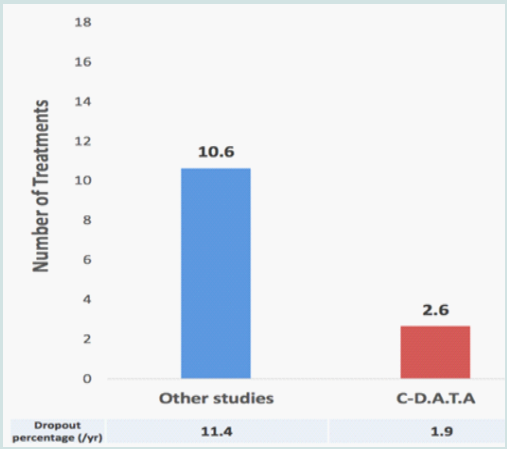

Figure 3: Follow-up period (in months) and change in best corrected visual acuity (ΔV) in C-DATA patients compared to patients from other studies.

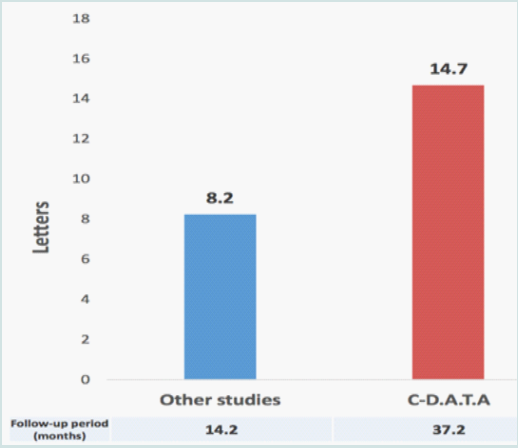

Figure 4: Dropout percentage per year (/yr) and difference in number of treatments per year (N) in C-DATA patients compared to patients in other studies.

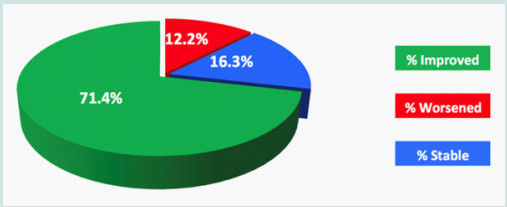

Figure 5: Percentage of eyes with improved (green color), worsened (red color), and stable vision (blue color).

and are more likely to comply with their course of treatment. This improved compliance is crucial for long-term management of a chronic condition like DME.

The success of C-DATA in this study challenges the one-size-fits-all approach often employed in DME management and other protocol-based studies [13]. By allowing for a more nuanced, responsive treatment strategy, C-DATA appears to optimize the use of available therapies (intravitreal injections, subtenon injections, and laser treatments) based on individual patient needs and responses. This personalized approach aligns with the broader trend towards precision medicine in healthcare. For DME, a condition known for its variability in presentation and treatment response, such tailored strategies are, therefore, particularly beneficial.

While these results are promising, it's important to acknowledge potential limitations of the study. The sample size, while sufficient to demonstrate significant differences, is relatively small. Larger, multi-center studies would be valuable to confirm these findings and explore their generalizability across diverse patient populations. Additionally, longer-term follow-up could provide insights into the durability of visual gains and the long-term safety profile of the C-DATA approach. This study was concluded before some newer VEGFs were introduced, but it is very easy to incorporate any new treatment into C-DATA, because it is a strategy (approach) not a treatment. Future research might also explore the potential of integrating advanced imaging technologies or artificial intelligence to further refine and personalize treatment algorithms.

Conclusion

The C-DATA approach represents a promising advancement in the management of DME. By offering improved visual outcomes, reduced treatment burden, and enhanced patient compliance, it addresses several key challenges in current DME care. As we continue to seek ways to optimize outcomes for patients with this complex condition, the principles of personalized, responsive treatment exemplified by C-DATA may well shape the future of DME management. The promising results of C-DATA in DME management have prompted its application to other medical conditions. Currently, we are evaluating the efficacy of this algorithmic approach in the treatment of wet age-related macular degeneration (AMD), with data collection ongoing and publication of results anticipated in the near future. Other applications of the C-DATA concept have also been explored in non-ophthalmic fields [13]. This expansion of C-DATA to diverse medical conditions shows its potential as a versatile and adaptable framework for personalized treatment across various specialties, extending well beyond ophthalmology.

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