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Efficacy and safety of corticosteroids versus standard therapy in alleviating diabetic retinopathy among Chinese patients with uncontrolled diabetes

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Abstract: To compare the effectiveness and safety profiles of corticosteroids versus standard therapy in alleviating diabetic retinopathy among Chinese patients with uncontrolled diabetes. Chinese diabetes patients aged more than 18 years with diabetic retinopathy were enrolled. Subjects who met the eligibility criteria were enrolled and were given either corticosteroid (Dexamethasone 1mg Intravenously or Intramuscularly per day in divided doses every 12 hours) or standard therapy (Ranibizumab 0.5-mg monthly injection) for 2 months. A total of 200 enrolled patients completed the study. Compared to Ranibizumab group, patients treated with Dexamethasone had almost similar proportion of eye with complete resolution (86% vs 85%, p>0.005) and similar improvement in height of subretinal fluid was observed in Dexamethasone- treated patients as compared to Ranibizumab-treated patients (91.2[32.4] vs 94.5 [27.4]; p>0.005). Patients treated with Ranibizumab had slightly greater improvement in lesion size, central macular thickness, best-corrected visual acuity as compared to Dexamethasone, however, the difference was not statistically significant. Overall, the results of the present study suggested that efficacy of Ranibizumab was almost similar to Dexamethasone in diabetic retinopathy among Chinese patients with uncontrolled diabetes. Ranibizumab was numerically more effective than Dexamethasone in Chinese diabetes patients with retinopathy. However, both study drugs were statistically similar with respect to the results of primary and secondary efficacy endpoints.

Keywords: Ranibizumab, Dexamethasone, retinopathy, diabetes.

INTRODUCTION

The prevalence of diabetes retinopathy across worldwide is rapidly growing at alarming rate, with estimated incidence at 5.8 per 100000 individuals, approximately 6 times higher incidence among men as compared to women (Liew *et al.*, 2013; Semeraro *et al*., 2019; Liu *et al*., 2016; Chatziralli *et al*., 2017; Loo *et al*., 2002). Although the exact cause of diabetes retinopathy is not clear and current treatment are mainly focus on subretinal fluid (SRF), choroidal vascular hyperpermeability, choroidal thickening, SRF height, lesion size and visual acuity. The patient with acute diabetes retinopathy had good diseases prognosis, with incidence of relapse among 60% of the patients (Ma *et al*., 2014; Lu *et al*., 2016; Salehi *et al*., 2015; Lim *et al*., 2014). Nevertheless, the recurrent diabetes retinopathy can result in permanent visual loss, therefore, efficacious and safe treatment modalities is critical.

There are number of therapeutic treatment options available for management of diabetes retinopathy that includes acetazolamide, anti-vascular endothelial growth factor (VEGF) therapy, rifampicin, photo therapy and anti-glucocorticoid (Lu *et al*., 2016; Salehi *et al*., 2015; Lim *et al*., 2014; van *et al*., 2018). It was also reported that the use of Dexamethasone in patients with retinopathy was effective in diabetic macular edema (Mojca *et al*., 2019; Jorge *et al*., 2019). However, there was no study investigating long-term safety and efficacy of Dexamethasone in patients with retinopathy. Pre-clinical evidences suggested the use of corticosteroids in treatment of diabetes retinopathy and clinical reports suggested that there was favorable outcome among patient with diabetes retinopathy after using corticosteroids (Mojca *et al*., 2019; Jorge *et al*., 2019). However, long-term safety and efficacy of corticosteroids has not been evaluated in clinical practices.

The present study was designed to compare the effectiveness and safety profiles of Dexamethasone versus Ranibizumab in alleviating diabetic retinopathy among Chinese patients with uncontrolled diabetes.

MATERIALS AND METHODS

Inclusion criteria

Chinese diabetes patients aged more than 18 years with diabetic retinopathy among Chinese patients with uncontrolled diabetes were enrolled during March 2022 to Nov 2022. The patients were eligible if they had persistent increased level of SRF for >3 months.

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Exclusion criteria

The patients were excluded if had history of optic nerve diseases and /or receiving any other therapy for retinopathy and /or the patients with hypotension, hyperkalemia, kidney disease and pregnancy. Each patient was informed about the off-label use of oral Dexamethasone at the time of informed consent process. Also, the patients with history of severe renal impairment, liver disease, lung disease, severe coronary artery disease (CAD) and thyroid disease were excluded. Moreover, the patients with any other pathology likely to affect the study outcomes, and patients who received concomitant and contra-indicated medications, as well as patients undergoing any other form of surgery were excluded.

Ethics

Written informed consent was obtained from each enrolled patient. The study received approval from the institutional ethics committee of Wuxi People's Hospital of Nanjing Medical University vide approval no. IEC-2022/Jan-2234-AN/E23. The procedures followed in the study were in line with the ethical principles laid down in the Helsinki Declaration and its later amendments.

Treatments and procedures

Subjects who met the eligibility criteria were enrolled and administered either corticosteroid (Dexamethasone 1mg Intravenously or Intramuscularly per day in divided doses every 12 hours) or standard therapy (Ranibizumab 0.5mg monthly injection) for 6 months. Each enrolled patient was carefully monitored and followed up for 6 months.

Assessment of efficacy and safety profiles

Baseline characteristics of each patient was assessed. The primary outcome of interest measured was number of patients/percentage of eyes with complete resolution of SRF during study period (6 months). The secondary outcome of interest measured were changes in height of SRF from baseline, changes in central macular thickness (CMT) from baseline, changes in lesion size from baseline and changes in best-corrected visual acuity from baseline. Also, the safety profile of both the study drugs were evaluated.

STATISTICAL ANALYSIS

No formal sample size calculation was performed in this study, since it was designed as a pilot study. Appropriate method was used to analyse data based on type and distribution (normal and non-normal). Data were analysed using Graph Pad (version 9.4.1) software. Significant difference was assumed at $p<0.05$. Quantitative data were analyzed using unpaired/paired t test or Mann Whitney/Wilcoxon test; whereas qualitative data were analyzed using chi-square/fisher exact test.

RESULTS

A total of 200 patients (100 patients in each group) were enrolled and all patients completed the study. The demography and baseline characteristics of patients in both treatments groups were comparable, as shown in table 1.

A summary of primary outcomes is presented in table 2. Patients treated with Dexamethasone had almost similar proportion of eye with complete resolution as compared to the patients with Ranibizumab. The difference was statistically not significant. Moreover, the number of eye with no SRF resolution was similar in patients treated with Ranibizumab as compared to the patients with Dexamethasone. This demonstrate that the Ranibizumab had numerically better efficacy in terms of complete resolution of SRF as compared to Dexamethasone.

A summary of secondary efficacy endpoint (SRF height, µm) is shown in table 3. Patients treated with Ranibizumab had slightly greater improvement in height of SRF as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, higher improvement in height of SRF was observed in Ranibizumab- treated patients as compared to Dexamethasone-treated patients. This demonstrate that the Ranibizumab showed numerically better efficacy in terms of SRF height as compared to Dexamethasone (table 3).

A summary of secondary efficacy endpoint (CMT height, µm) is shown in table 4. Patients treated with Ranibizumab had greater improvement in CMT as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, higher improvement in CMT was observed in Ranibizumab- treated patients as compared to Dexamethasone-treated patients. This demonstrate that the Ranibizumab showed numerically better efficacy in terms of CMT as compared to Dexamethasone (table 4).

A summary of secondary efficacy endpoint (lesion size, µm) is shown in table 5. Patients treated with Ranibizumab had greater improvement in lesion size as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, higher improvement in lesion size was observed in Ranibizumab-treated patients as compared to Dexamethasone-treated patients. This demonstrate that the Ranibizumab showed numerically better efficacy in terms of lesion size as compared to Dexamethasone (table 5).

A summary of secondary efficacy endpoint (best-corrected visual acuity, µm) is shown in table 6. Patients treated with Ranibizumab had greater improvement in

Table 1: Baseline characteristics of patients

Characteristic	Dexamethasone (n=100)	Ranibizumab (n=100)	P value
Median age (years)	59	58	>0.05
Female sex (%)	48	51	>0.05
Disease durations (months), mean (SD)	5.2±2.4	5.4±2.6	>0.05
SRF, µm, mean (SD)	234±85.1	239±83.2	>0.05
CMT, µm, mean (SD)	367.2± 221	372.1±287	>0.05
Lesion size, µm, mean (SD)	2738.3±134	2762±228	>0.05
Best-corrected visual acuity (log MAR)	0.64±0.43	0.69±0.47	>0.05

Table 2: Summary of comparison of eye with complete resolution of SRF in both groups

Characteristic	Dexamethasone (n=100)	Ranibizumab (n=100)	*P*
Resolution of SRF (complete)	87(87 %)	81(81%)	>0.05
1 month	23	21	
3 month	24	20	
6 moths	40	40	
No complete resolution of SRF	13(13%)	19(13%)	>0.05

Values of *p* based on categorical variables were calculated using Chi-square test.

Table 3: Summary of secondary efficacy endpoint (SRF height, µm) in the two groups

Characteristic	Dexamethasone (n=100)	Ranibizumab (n=100)	*P*
1 month	189.2 ± 122.4	179.3 ± 144.8	>0.05
3 month	142.3 ± 98.3	138.2 ± 102.6	>0.05
6 months	87.2 ± 72.5	83.5 ± 73.1	>0.05

Values of *p* based on categorical variables were calculated using Mann Whitney test.

best-corrected visual acuity as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, higher improvement in best-corrected visual acuity was observed in Ranibizumab-treated patients as compared to Dexamethasone-treated patients.

This demonstrate that the Ranibizumab showed numerically better efficacy in terms of best-corrected visual acuity as compared to Dexamethasone (table 6).

DISCUSSION

In China, there was no study comparing long term efficacy of dexamethasone versus ranibizumab in alleviating diabetic retinopathy among Chinese patients with uncontrolled diabetes. This is the first clinical study carried out to evaluate the long term efficacy profiles of Dexamethasone versus Ranibizumab in diabetes patients with retinopathy. The findings are consistent with those reported in previous studies in which Ranibizumab showed significantly reduced the risk of diabetic retinopathy progression among patient with diabetic, and several ranibizumab-treated eyes showed significant improvements in severity of diabetic retinopathy (Michael *et al*., 2012; John *et al*., 2016; Irini, 2021; Chatziralli, 2021; Antoszyk *et al*., 2020; Li *et al*., 2022; Maguire *et al*., 2021; Wang *et al*., 2022; Liberski *et al*., 2022; Türkseven *et al*., 2021). Another study reported that ranibizumab improved eye vision among diabetes patients, however efficacy of ranibizumab is depends on the baseline visual acuity.

Several line of clinical evidences reported that ranibizumab in patients with diabetic retinopathy was found effective, safe and demonstrates significant improvement of severity of diabetic retinopathy. However, still no agreement in scientific community regarding the treatment management guideline among patients with diabetic retinopathy, whereas the benefits of ranibizumab on the advancement of retinal ischemia remains imprecise (Paine *et al*., 2021; Tsai *et al*., 2021; Nawar *et al*., 2022; Bıçak *et al*., 2022; Chiang *et al*., 2021; Toscano *et al*., 2021) .

In our study, patients treated with ranibizumab had slightly greater proportion of eye with complete resolution as compared to the patients with Dexamethasone. The difference was not statistically significant. Moreover, number of eye with no complete resolution SRF was slightly higher in patients treated with ranibizumab as compared to the patients with

Table 4: Summary of secondary efficacy endpoint (CMT, µm) in the two groups

Characteristic	Dexamethasone (n=100)	Ranibizumab (n=100)	*P*
1 month	234.1 ± 121.4	232.2 ± 108.2	>0.05
3 month	256.4 ± 113.1	243.1 ± 128.1	>0.05
6 moths	249.3 ± 87.3	234.2 ± 83.2	>0.05

Values of *p* based on categorical variables were calculated using Mann Whitney test.

Table 5: Summary of secondary efficacy endpoint (lesion size, µm) in the two groups

Characteristic	Dexamethasone (n=100)	Ranibizumab (n=100)	*P*
1 month	1891.1± 123.1	1743.2 ± 124.3	>0.05
3 month	2104.4 ± 340.7	2003.3 ± 408.4	>0.05
6 moths	1767.1 ± 124.4	1652.3 ± 234.1	>0.05

Values of *p* based on categorical variables were calculated using Mann Whitney test.

Table 6: Summary of secondary efficacy endpoint (best-corrected visual acuity, µm) in the two groups

Characteristic	Dexamethasone (n=100)	Ranibizumab (n=100)	*P*
1 month	0.36 ± 0.83	0.42 ± 0.41	>0.05
3 month	0.42 ± 0.41	0.41 ± 0.32	>0.05
6 moths	0.32 ± 0.34	0.32 ± 0.43	>0.05

Values of *p* based on categorical variables were calculated using Mann Whitney test.

Dexamethasone. Also, the patients treated with ranibizumab had slightly greater improvement in height of SRF as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, higher improvement in height of SRF was observed in ranibizumab- treated patients as compared to Dexamethasone-treated patients.

Patients treated with ranibizumab had greater improvement in CMT as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, greater improvement in CMT was observed in ranibizumab-treated patients as compared to Dexamethasone-treated patients. Patients treated with ranibizumab had greater improvement in lesion size as compared to Dexamethasone. The difference was statistically not significant at each time point. At 1, 3 and 6 months, higher improvement in lesion size was observed in ranibizumab-treated patients as compared to Dexamethasone-treated patients. Patients treated with ranibizumab had greater improvement in best-corrected visual acuity as compared to Dexamethasone. The difference was not statistically significant at each time point. At 1, 3 and 6 months, higher improvement in best-corrected visual acuity was observed in ranibizumab-treated patients as compared to Dexamethasone-treated patients. This demonstrate that the ranibizumab showed numerically better efficacy as compared to Dexamethasone.

It was reported that Dexamethasone act on retinal thickness and has been reported that peak effect was observed after 2 months of treatments (Mojca *et al*., 2019; Jorge *et al*., 2019). However, long-term efficacy of Dexamethasone has not been evaluated in clinical practices. Moreover, several studies showed that Dexamethasone do not have any significant role among patients with diabetic retinopathy. Compared to Dexamethasone, it was also reported the use of ranibizumab was effective in accelerating the recovery of visual acuity and promote the recovery (Irini *et al*., 2021; Chatziralli, 2021; Antoszyk *et al*., 2020; Li *et al*., 2022; Maguire *et al*., 2021; Wang *et al*., 2022; Liberski *et al*., 2022; Türkseven *et al*., 2021; Paine *et al*., 2021). However, there was no studies investigating long-term efficacy of ranibizumab versus Dexamethasone among Chinese patients. Also, there is no head to head study comparing the efficacy and safety of ranibizumab versus Dexamethasone in patients with diabetic retinopathy. Therefore, the present was designed to compare the effectiveness of ranibizumab versus Dexamethasone in patients with diabetic retinopathy.

Overall, the results of the present study suggest that ranibizumab is more effective than Dexamethasone in Chinese diabetes patients with diabetic retinopathy. Overall, both study drugs were statistically similar with respect to primary and secondary efficacy endpoints. Numerically, ranibizumab was more effective than Dexamethasone in Chinese diabetes patients with diabetic retinopathy. The possible reason for the non-significant

differences in clinical outcomes between the two groups may be due to the low sample size used in the study.

Limitations of the study

The results of this study may not be generalized to the Chinese population due to the low sample size used. Thus, a study with large sample size is required to validate the results reported here.

CONCLUSION

This study has demonstrated that ranibizumab was slightly more effective than Dexamethasone in Chinese diabetes patients with diabetic retinopathy. However, Ranibizumab and Dexamethasone were statistically similar with respect to primary and secondary efficacy endpoints. Our study results encourage to design large multi-centric, parallel, and active control study to confirm the finding of present study.

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