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ORIGINAL ARTICLE

Sodium-Glucose Cotransporter-2 Inhibitors Utilization and Outcomes in Patients with Chronic Kidney Disease at a Tertiary Centre

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ABSTRAK

Perencat sodium-glucose cotransporter-2 (SGLT2) merupakan sejenis agen antidiabetik yang mempunyai fungsi perlindungan kepada jantung dan buah pinggang. Selain itu, ia menghalang penyerapan sodium pada bahagian tubular dan mengurangkan tekanan intraglomerular pada buah pinggang. Kebelakangan ini, penggunaan perencat SGLT semakin meningkat tanpa mengira status kencing manis dalam kalangan pesakit buah pinggang kronik. Walau bagaimanapun, data sejagat mengenai penggunaan perencat SGLT2 masih terhad. Kami menjalankan kajian deskriptif dalam kalangan pesakit buah pinggang kronik yang menggunakan perencat SGLT2 di Klinik Nefrologi. Sebanyak 156 orang pesakit telah diberikan preskripsi perencat SGLT2 bermula tahun 2017 sehingga 2022. Daripada jumlah tersebut, 58.3% adalah lelaki dengan umur purata 61 ± 13 tahun dan 86.5% mempunyai kencing manis, dengan kadar purata 'estimated glomerular filtration rate' (eGFR) 46.41 ± 21.14 ml/min/1.73m^2 dan proteinuria 2.22 ± 2.62 g/hari. Sebanyak 85.9% daripada jumlah pesakit turut menggunakan penyekat 'renin angiotensin-system' (RAS), manakala kebanyakan pesakit yang tidak menggunakan penyekat RAS adalah pesakit buah pinggang kronik peringkat 4. Dalam kalangan pesakit bukan kencing manis, sebanyak 81% mempunyai glomerulonefritis, iaitu separuh daripadanya adalah IgA nefropati dan 42.9% pesakit menggunakan immunosupresi. Terdapat pembantutan yang signifikan pada kadar penurunan eGFR dalam tempoh 6 bulan penggunaan perencat SGLT2 iaitu daripada -3.46 ± 6.56 ml/min/1.73m^2 kepada -0.77 ± 7.97 ml/min/1.73m^2 (p=0.001). Di samping itu, pembantutan terhadap kadar penurunan eGFR yang ketara turut ditunjukkan oleh

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pesakit buah pinggang pada peringkat yang lebih tinggi. Walau bagaimanapun, kadar penurunan proteinuria adalah tidak ketara sepanjang tempoh 6 bulan (-0.03 ± 2.31 g/hari. Setakat ini tiada laporan mengenai kesan sampingan perencat SGLT2 dikenalpasti. Kesimpulannya, perencat SGLT2 melambatkan kadar penurunan eGFR dengan pengurangan kadar proteinuria secara minimum dalam jangka masa pendek. Data mengenai keberkesanan dan keselamatan jangka masa panjang perencat SGLT2 dalam populasi tempatan memerlukan penilaian lanjut.

Kata kunci: Penyakit ginjal kronik; perencat SGLT2; proteinuria

ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitor is an antidiabetic agent with cardiac and renal protective properties. Its renal protective property is a result of the inhibition of tubular sodium reabsorption and reduction in the intraglomerular pressure. The use of SGLT2 inhibitor in chronic kidney disease (CKD) independent of diabetic status is emerging. However, the real-world data of SGLT2 inhibitor utilisation in CKD is limited. We conducted a descriptive study of patients with CKD, who were prescribed with SGLT2 inhibitor in our Nephrology Clinic. A total of 156 patients were initiated on SGLT2 inhibitor from 2017 to 2022. Among them, 58.3% were male, with a mean age of 61 ± 13 years, and 86.5% had diabetes mellitus, with estimated mean glomerular filtration rate (eGFR) of 46.41 ± 21.14 ml/min/1.73m^2, and proteinuria of 2.22 ± 2.62 g/day. A total of 85.9% of patients were on renin-angiotensin-system (RAS) blockers, whereby those who were not prescribed with RAS were mostly CKD stage 4. Among the non-diabetic patients, 81% had glomerulonephritis, half of which was IgA nephropathy, and 42.9% were on immunosuppressants. There was a significant retardation of eGFR decline over a six-month-duration after the initiation of SGLT2 inhibitor from -3.46 ± 6.56 ml/min/1.73m^2 to -0.77 ± 7.97 ml/min/1.73m^2 (p=0.001). The retardation of eGFR decline was more pronounced in more advanced CKD stages. However, the proteinuria reduction was insignificant over a six-month-duration (-0.03 ± 2.31 g/day). There were no adverse events reported. In conclusion, SGLT2 inhibitor retarded the eGFR decline with minimal proteinuria reduction in short-term. Nonetheless, long-term efficacy and safety data of SGLT2 inhibitor in local populations requires further evaluation.

Keywords: Chronic kidney disease; proteinuria; SGLT2 inhibitors

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitor is an oral antidiabetic agent. It reduces the blood plasma glucose and body weight by promoting urinary glucose and calorie excretion through the inhibition of renal tubular glucose reabsorption in the proximal tubule. The SGLT2 in the renal proximal tubule is the major pathway of reabsorption of glucose filtered from glomerulus, which is around 160-180 g/day and can be two-to-three-fold higher in hyperglycaemia (Vallon 2015).

Apart from its antidiabetic property, SGLT2 inhibitor was found to have cardiac and renal protective properties in many large-scale clinical trials recent years (Zelniker et al. 2019). With the natriuresis and osmotic diuresis induced by SGLT2 inhibitor, it is not difficult to understand its cardiac protective function through a reduction in cardiac preload and afterload. Several theories have been postulated to further explain the cardiac protective property of SGLT2 inhibitor, which include the improvement in cardiac metabolism and bioenergetics, myocardial sodium and hydrogen exchange inhibition, reduction of necrosis and cardiac fibrosis, alteration in adipokines, cytokine production and epicardial adipose tissue mass (Verma & McMurray 2018).

The renal protective property of SGLT2 inhibitor is realised by the reduction of intraglomerular pressure. This can be achieved by glomerular efferent vasodilation through a tubuloglomerular feedback from high intratubular sodium due to the inhibition of sodium reabsorption in the proximal tubules (Hou et al. 2020). With the understanding of its renal protective mechanism, SGLT2 inhibitor has been further evaluated for its use in non-diabetic chronic kidney disease (CKD) patients and proven to be beneficial in large-scale clinical trials (EMPA-Kidney Collaborative Group 2023; Patel et al. 2021). This clinical evidence promotes SGLT2 inhibitor prescription in patients with CKD independent of diabetic status. However, the real-world data of SGLT2 inhibitor utilisation in CKD is limited worldwide, and none in Malaysia.

MATERIALS AND METHODS

This is a single-centre, retrospective, cohort study. All patients who had CKD and were prescribed SGLT2 inhibitor in Nephrology Clinic, Hospital Canselor Tuanku Muhriz between January 2017 and December 2022 were included. We excluded those who had lost to follow-up, without laboratory investigations, and initiated SGLT2 inhibitor in other clinic such as Endocrinology or Cardiology Clinic.

All recruited patients were reviewed for their baseline characteristics, which include demographic data, comorbidities particularly diabetes mellitus, medications, primary renal disease, and renal function in terms of estimated glomerular filtration rate (eGFR) and proteinuria. The eGFR and proteinuria of patients six months prior, immediately prior, one-to-three-month after, and six months after

initiation of SGLT2 inhibitor were compared to calculate the eGFR decline and proteinuria progression. The differences between the six-month eGFR decline prior and after SGLT2 inhibitor were calculated.

In the present study, Statistical Product and Service Solution (SPSS, Chicago, IL, USA) software version 26 was used for data analysis. Descriptive statistics was used to present the background and study variables. Paired T-test was used to calculate and compare the eGFR decline and proteinuria progression prior to and after SGLT2 inhibitor prescription.

RESULTS

A total of 156 patients were enrolled in this study. The prescriptions of SGLT2 inhibitor had an increasing trend from one in 2017 and 2018, to three in 2019, 16 in 2020, 27 in 2021, then a sudden surge of prescriptions to 108 in 2022. There was a slight male predominance (58.3%) in the cohort, and majority of patients were Malays (63.5%). The mean (± standard deviation) age of the patients was 61.19 ± 13.03 years. A total of 86.5% (n = 135) of patients had diabetes mellitus. Among the non-diabetic patients (n = 21), 81% had glomerulonephritis, half of which was IgA nephropathy, and 42.9% of them were on immunosuppressants. 85.9% (n = 134) of patients were on renin-angiotensin-system (RAS) blockers before the prescription of SGLT2 inhibitor, those who were not prescribed were mostly CKD stage 4.

At baseline, majority of the patients had CKD stage 3B and 4, 37.8% and 21.2%, respectively. The mean eGFR was 46.41 ± 21.14 ml/min/1.73m^2 with a mean proteinuria of 2.22 ± 2.62 g/day. Prior to the initiation of SGLT2 inhibitor, the mean eGFR decline over a six-month-duration was -3.46 ± 6.56 ml/min/1.73m^2. There was a significant retardation of eGFR decline over a six-month-duration after the prescription of SGLT2 inhibitor to -0.77 ± 7.97 ml/min/1.73m^2 with a p-value of 0.001 (Figure 1). The eGFR decline retardation was more pronounced in more advanced CKD stages (Figure 2). There was a retardation in proteinuria

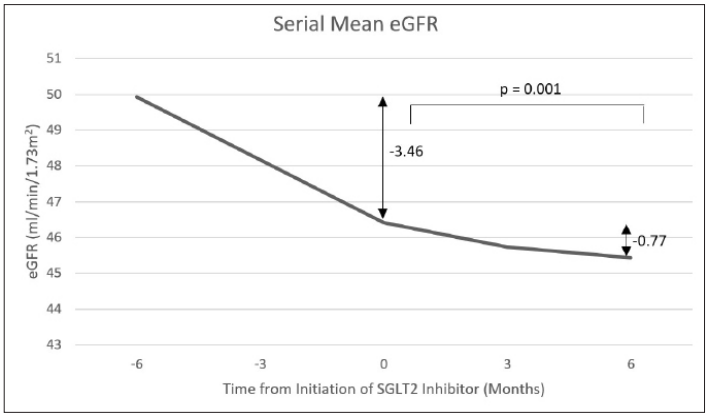

FIGURE 1: Serial mean estimated glomerular filtration rate

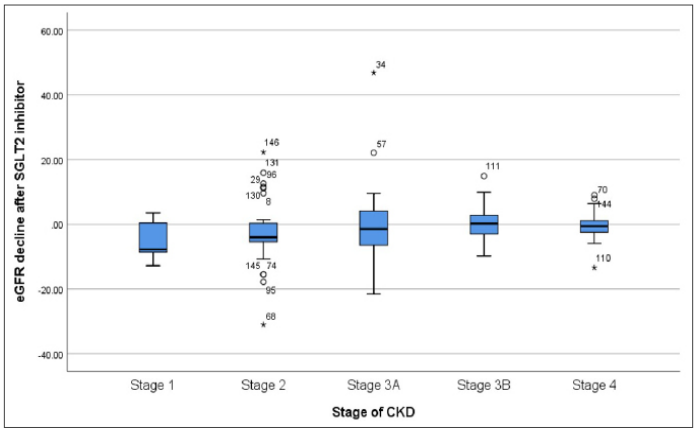

FIGURE 2: Estimated glomerular filtration rate decline over a six-month-duration after the initiation of sodium-glucose cotransporter-2 inhibitor

progression with minimal proteinuria reduction of -0.03 ± 2.31 g/day over a six-month-duration. However, it was not statistically significant with a p-value of 0.132 (Figure 3). There were no adverse events reported. Table 1 summarised the demographic and clinical data of our patients.

DISCUSSION

SGLT2 inhibitor is undoubted to be one of the renal protective medications proven to retard CKD progression independent of diabetic status (EMPA-Kidney Collaborative Group 2023; Patel et al. 2021). Despite this known fact, the utilisation of SGLT2 inhibitor worldwide is still suboptimal (Arnold et al. 2022). This could be possibly due to the fear of adverse effects such as euglycemic ketoacidosis, genitourinary infections, acute kidney injury (AKI) and the lack of resources in developing countries. However, the use of SGLT2 inhibitor in Malaysia depends on the

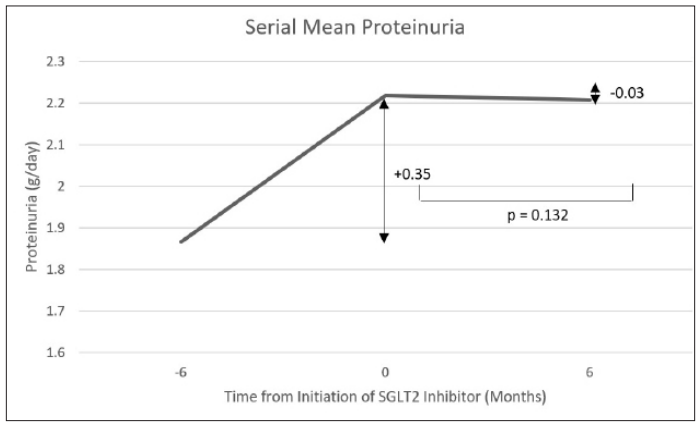

FIGURE 3: Serial mean proteinuria

TABLE 1: Demographic and clinical data of patients

Characteristics	Total (n = 156)	Diabetic (n = 135)	Non-Diabetic (n = 21)
Gender no. (%)			
Male	91 (58.3)	82 (60.7)	9 (42.9)
Female	65 (41.7)	53 (39.3)	12 (57.1)
Ethnicity no. (%)			
Malay	99 (63.5)	84 (62.2)	15 (71.4)
Chinese	47 (30.1)	41 (30.4)	6 (28.6)
Indian	8 (5.1)	8 (5.9)	0 (0.0)
Other	2 (1.3)	2 (1.5)	0 (0.0)
Age (years)	61.19 ± 13.03	62.85 ± 12.02	50.52 ± 14.48
Primary Renal Disease no. (%)			
Diabetic kidney disease*	118 (75.7)	118 (87.4)	0 (0.0)
IgA nephropathy	16 (10.3)	6 (4.4)	10 (47.6)
Lupus nephritis	9 (5.8)	6 (4.4)	3 (14.3)
ANCA-associated nephropathy	1 (0.6)	0 (0.0)	1 (4.8)
Focal segmental glomerulosclerosis	4 (2.6)	3 (2.2)	1 (4.8)
Membranous glomerulonephritis	2 (1.3)	1 (0.7)	1 (4.8)
Membranoproliferative glomerulonephritis	2 (1.3)	1 (0.7)	1 (4.8)
Hypertensive nephrosclerosis	4 (2.6)	0 (0.0)	4 (19.0)
Renin-angiotensin-system blockers no. (%)			
Yes	134 (85.9)	113 (83.7)	21 (100.0)
No	22 (14.1)	22 (16.3)	0 (0.0)
Immunosuppressants no. (%)			
Yes	24 (15.4)	15 (11.1)	9 (42.9)
No	132 (84.6)	120 (88.9)	12 (57.1)
Chronic kidney disease stage no. (%)			
Stage 1	7 (4.5)	5 (3.7)	2 (9.5)
Stage 2	28 (17.9)	21 (15.6)	7 (33.3)
Stage 3A	29 (18.6)	26 (19.3)	3 (14.3)
Stage 3B	59 (37.8)	52 (38.5)	7 (33.3)
Stage 4	33 (21.2)	31 (23.0)	2 (9.5)
Stage 5	0 (0.0)	0 (0.0)	0 (0.0)
Baseline eGFR (ml/min/1.73m2)	46.41 ± 21.14	44.83 ± 20.56	56.52 ± 22.52
Baseline proteinuria (g/day)	2.22 ± 2.62	2.29 ± 2.78	1.74 ± 1.01
eGFR decline prior (ml/min/1.73m2)	-3.46 ± 6.56	-3.18 ± 6.23	-5.28 ± 8.30
eGFR decline early post (ml/min/1.73m2)	-1.40 ± 6.28	-1.48 ± 6.07	-0.83 ± 7.62
eGFR decline post (ml/min/1.73m2)	-0.77 ± 7.97	-0.58 ± 8.09	-1.99 ± 7.24
Proteinuria progression prior (g/day)	0.35 ± 1.66	0.41 ± 1.72	-0.003 ± 1.23
Proteinuria progression post (g/day)	-0.03 ± 2.31	-0.03 ± 2.43	-0.03 ± 1.39

Continuous values are mean ± standard deviation; discrete values are n (%); *4 patients had renal transplant done; eGFR = estimated glomerular filtration rate.

affordability of patients to purchase the medication. This is translated into a lacking of real-world data of SGLT2 inhibitor use.

The prescription of SGLT2 inhibitor in our centre has increased over the years due to the emergence of clinical evidence with a shift of prescription in diabetic to non-diabetic CKD patients. To date, there is no reported

adverse events in our centre. Despite conflicting data published regarding the potential risk of AKI, many large-scale clinical trials have assured the safety of SGLT2 inhibitors (Copur et al. 2022). In fact, those patients who had an eGFR dip after the initiation of SGLT2 inhibitor were found to have a reduction in eGFR decline with a better renal survival later (Heerspink et al. 2020).

Nonetheless, the benefits and risks of using SGLT2 inhibitors might vary in different populations. A screening tool was developed to predict the incidence of genitourinary adverse events in SGLT2 inhibitors (Unadkat et al. 2020). However, the risk of euglycemic ketoacidosis and AKI is still unpredictable. More real-world data of SGLT2 inhibitor usage is needed to study the predictive factors associated with its risks and benefits, in order to guide the physicians in its prescription. The present study was the first real-world data of SGLT2 inhibitor use in CKD patients in Malaysia, which demonstrated a significant retardation in eGFR decline especially in more advanced CKD stages. Similar findings were demonstrated by our neighbour country (Liu et al. 2022). However, there was no significant reduction in proteinuria over a short-term six-month-duration as postulated in various literature (Perico et al. 2017; Sternlicht & Bakris 2020). This could possibly be due to the effect of proteinuria reduction can only be appreciated after a longer duration of SGLT2 inhibitor (Cherney et al. 2020) or in patients with heavier proteinuria (Jardine et al. 2021; Delanaye et al. 2021). Hence, a long-term study with a wider range of proteinuria and CKD stages is required to further evaluate the long-term efficacy and safety data of SGLT2 inhibitor in local populations.

CONCLUSION

SGLT2 inhibitor is safe to be used in CKD patients. It retarded the eGFR decline with minimal proteinuria reduction in short-term. Nonetheless, long-term efficacy and safety data of SGLT2 inhibitor in local populations requires further evaluation.

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