Despite being Apparently Equal, Concentrated Lispro-200 Performs Metabolically and Subjectively Better than Lispro-100

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ABSTRACT

Aims: The aim of the study was to evaluate whether freshly available concentrated U-200 lispro insulin performed equally to previously marketed U-200 insulin lispro in terms of glycemic control and patient satisfaction.

Methods: 360 outpatients with type 2 diabetes (T2DM) having self-injected U-100 lispro Kwikpen (KP) before meals for a long time were randomly selected to either going on with their usual treatment schedule (control group, n=180, CG) or switching to U-200 lispro KP for 12-weeks (treated group, n=180, TG) and filling in a treatment satisfaction questionnaire at the end of the observation period. They were all assessed for changes in body weight, blood pressure, BMI, fasting blood glucose, HbA1c, total cholesterol, HDL cholesterol, tryglicerides, uric acid, creatinine clearance rate with respect to baseline.

Results: No significant changes were observed in the CG. Conversely, the TG displayed significantly decreased hypoglycemic episodes (p<0.01), as well as, fasting plasma glucose levels and glucose variability (p<0.01) compared to baseline. According to the questionnaire, 60 to 81% TG people were very satisfied with U-200 lispro KP and most of them preferred to stick to the new insulin preparation.

Conclusions: hypoglycemic event rates, fasting blood glucose, glycemic variability and subjective ratings significantly improved in people treated with U-200 lispro. Diversity in both molecular insulin concentration and injection device engineering showed to provide better results in U-200 treated patients utilizing the same drug as controls.

Keywords: lispro U-200; insulin; device; diabetes; adherence

Introduction

Compared to times when only syringes and vials were available, a major technological progress was represented by the development of pens. Indeed, these devices allowed greater patient adherence and higher flexibility, along with greater precision and ease of use, satisfaction and better quality of life [1-5]. The preference for pens was assessed by many studies involving both inpatients and healthcare staff members [6-8].

The reason why pens immediately and widely spread out among people with diabetes mostly relies on their beneficial and easy-to-handle features in the patient’s eyes (in terms of transportation and use, for instance) as well as on their proven dose accuracy. It also appears to be related to the smaller size of associated needles as compared to those meant for syringes [1].

Their success also depends on continuing technological advances in terms of shorter and thinner needles granting less painful injections and on continuous improvement of device engineering. Apropos of this, it is worth recalling that the key elements for getting the best clinical results and gaining maximum adherence from users are: 1) dose accuracy and repeatability; 2) ease of use; 3) patient-customization.

Nevertheless, despite entailing great advantages in disease management, dose accuracy and treatment adherence, pen utilization is no guarantee of correct insulin shots. This becomes even more relevant in patients on Basal-Bolus or Basal-Plus regimens, whose required injection rate is quite high.

The main issues related to insulin injections can be summarized as follows:
Pen utilization

KwikPen® (KP) entered the market well in advance and has therefore been used for more years than FlexPen® (FP) and SoloStar® (SS) devices, which were also designed for both fast and basal analog administration and nowadays share with KP a worldwide utilization. Various experiences have shown how mechanical features of pens as well of needle length and gauge (G) can influence injection results in terms of dose accuracy and glide force, thus also affecting patient’s ease of use and comfort during insulin administration [9-20]. Moreover, both experimental studies and clinical practice data suggest that ergonomically relevant aspects of industrial design improve treatment adherence by positively influencing the dynamics of injection as for handling smoothness and reduced glide force and by thus enhancing individual ability to fully push the plunger down the whole distance required [10,14,21-24]. With respect to that, it is relevant to note that the engineering of the KP devoted to U-200 lispro administration was further improved in terms of both smoothness and glide force as compared to the previous device containing U-100 lispro.

Musculoskeletal problems at the hand level

Another major concern for patients trying to perform injections properly comes from musculo-skeletal changes involving their hands [25-27]. These can be evaluated by validated and objective tests based on a scoring system and exploring individual abilities to carry out everyday life activities (Jebsen-Taylor hand-function test: handling small and large objects, turning pages of a book, etc. [28,29]. Above mentioned changes are primarily related to the duration of the disease and to impaired metabolic control and include (i) diabetic keiroarthropathy or limited joint mobility (affecting 8-50% of people with diabetes vs. 0-26% of people without diabetes); (ii) flexor tenosynovitis (affecting 10-15% of people with diabetes vs. 1% of non-diabetic subjects); (iii) carpal tunnel syndrome (reported in 11-26% of patients with diabetes) [27].

Indeed musculo-skeletal changes might often cause troubles during injection so that people might stop well before pushing the plunger down the whole distance to the stop position. Therefore any devices delivering the same amount of drug in a smaller volume and requiring less glide force may be expected to improve injection performance and thus grant better glycemic control.

Local complications due to insulin injections

The most well-known complications associated with an incorrect injection techniques are nodules due to lipohypertrophy (LH). They consist of areas of thickened tissue developing and progressively enlarging within the subcutaneous adipose layer where insulin is repeatedly injected. LH causes unpredictable insulin absorption and this can result in poor metabolic control and in ever increasing insulin administration to try and overcome the problem [30,31].

A series of clinical and meta-analysis-derived data helped define the typical profile of LH-prone diabetic people, and we recently pointed out the following factors as strongly suggestive of LH: large insulin dose requirement, recurrent hypoglycemic episodes, unexplained glycemic variability, fast-growing diabetes complications, unsafe lifestyle, marital status, as well as, needle length/gauge/reuse and missing injection site rotation [32-36]. In particular our recent results underline a significant relationship between high insulin doses and risk of LH [36]. So far this has been a major problem per se and especially for patients inconsistently rotating injection sites as large daily insulin doses have been carrying along correspondingly high fluid volumes to be injected several times a day.

Concentrated insulin

Easy-to-handle concentrated insulins, which just recently became available, could have a positive impact on both personal feelings about injections and treatment adherence, thus further improving metabolic control.

Lispro U-200 and Lispro U-100 insulin preparations have superimposable pharmacokinetic profiles despite the former being concentrated twice as much as the latter [37]. This implies no dosage changes when shifting from one to the other as in fact bio-equivalence carries along dose-equivalence. However, by halving their injected volume when shifting from U-100 to U-200 Lispro, patients achieve a remarkable advantage in terms of force applied to the plunger per se. Indeed, by comparing sliding force at both a 30 U dosage and a 9 U/second injection speed through ThinWall (TW) and Extra Thin Wall (XTW) needles, Rees et al. [38] showed the U-200 KP to require a significantly lower thrust than the U-100 KP.

Based on the above mentioned issues, the expected primary endpoint of the study was glycemic control associated with U-200 as compared to U-100 insulin lispro over a 12-week observation period. As a secondary endpoint we analyzed patients’ ratings of the U-200 lispro KP utilization.

Subjects

The present study was carried out by a network of 10 identically organized outpatient diabetes centers (DCs) from a single institution called AID (Associazione Italiana Diabete) participating in the so called AMD Annals Initiative and previously documented to attain the same performance levels. After getting their database utilization approval by their local Ethics Committees, all DCs collected information only from patients preliminarily signing their informed consent to anonymous data utilization for clinical evaluations aimed at diabetes community health and quality of life improvement [39]. The study conformed to the Helsinki Declaration.

360 outpatients never reporting any cardio-vascular episodes and consecutively referring to our DCs for type 2 diabetes (T2DM) were enrolled for being on glargine as the long-acting analog and on U-100 lispro before each of the three meals since at least 3 months. As is our custom, all of them had been trained and regularly retrained to use 4 mm/32G needles, immediately dispose of them thereafter, consistently rotate injection sites
and accurately avoid LH areas according to the current best injection technique guidelines [30]. Their general features are reported in Table 1.

They were then evenly and randomly divided into a control group going on with the usual treatment schedule (n=180, CG) and a half-volume group (n=180, HVG) switching to U-200 lispro KP for 12-weeks in compliance with the usual national NHS reimbursement rules (i.e. without any external financial support) and filling in a treatment satisfaction questionnaire at the end of the observation period (Figure 1).

Both groups were assessed for changes from baseline in terms of body weight, blood pressure, BMI, fasting blood glucose, HbA1c, total cholesterol, HDL cholesterol, triglycerides, uric acid and creatinine clearance rate.

### Table 1: Baseline characteristics of the halved volume group (HVG) and the control group (CG) expressed as mean ± SD or as n. and percent rate in case of categorical variables. Differences between them did not reach statistical significance. 66 and 68 subjects had more than a single diabetes complication in the HVG and the CG, respectively; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HVG (n. 180)</th>
<th>CG (n. 180)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n. (%)</td>
<td>102 (57.4)</td>
<td>98 (54.4)</td>
<td></td>
</tr>
<tr>
<td>Age (years) M ± SD (Range)</td>
<td>60.2 ± 6.0</td>
<td>60.1 ± 5.9</td>
<td></td>
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<tr>
<td>BMI (kg/m²) M ± SD (Range)</td>
<td>28.5 ± 3.5</td>
<td>29.4 ± 1.0</td>
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<tr>
<td>Normal weight n. (%)</td>
<td>18 (9.5)</td>
<td>19 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Overweight n. (%)</td>
<td>113 (59.5)</td>
<td>104 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Obese n. (%)</td>
<td>59 (31.0)</td>
<td>57 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (years) M ± SD (Range)</td>
<td>8.6 ± 2.1</td>
<td>6.7 ± 2.0</td>
<td>4-9</td>
</tr>
<tr>
<td>SBP (M ± SD, mmHg)</td>
<td>130.2 ± 5.9</td>
<td>130.5 ± 6.1</td>
<td></td>
</tr>
<tr>
<td>DBP (M ± SD, mmHg)</td>
<td>78.7 ± 6.3</td>
<td>78.1 ± 6.0</td>
<td></td>
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<tr>
<td>Mean dose of lispro insulin (IU, M+SD)</td>
<td>48 ± 16</td>
<td>51 ± 18</td>
<td></td>
</tr>
<tr>
<td>Lipohypertrophy (%)</td>
<td>67</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>141.2 ± 19.5</td>
<td>147. ± 18.70</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.6 ± 0.9</td>
<td>7.7 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Severe Hypoglycemia (n/12weeks; M±SD)</td>
<td>5.2 ± 3.1</td>
<td>5.1 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Mild Hypoglycemia (n/12weeks; M±SD)</td>
<td>14 ± 6</td>
<td>16 ± 4</td>
<td></td>
</tr>
<tr>
<td>Glucose Variability (mg/dl; Δ min-max, M+SD)</td>
<td>167 ± 33</td>
<td>173 ± 41</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>181.3 ± 25.8</td>
<td>190.3 ± 23.2</td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>43.9 ± 8.1</td>
<td>42.5 ± 7.9</td>
<td></td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>104.9 ± 23.8</td>
<td>109.5 ± 24.0</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>163.4 ± 45.3</td>
<td>170.2 ± 44.5</td>
<td></td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9 ± 0.5</td>
<td>0.9 ± 0.4</td>
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<tr>
<td>eGFR ml/min/1.73m²</td>
<td>90.3 ± 17.9</td>
<td>91.2 ± 14.5</td>
<td></td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>45</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering treatment (%)</td>
<td>63</td>
<td>70</td>
<td></td>
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<tr>
<td>Antihypertensive treatment (%)</td>
<td>70</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>39</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Diabetes Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy BG (%)</td>
<td>11.8</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Nephropathy* (%)</td>
<td>9.4</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Autonomic Neuropathy (%)</td>
<td>10.0</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy (%)</td>
<td>10.6</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>Other local Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthrosis of the hand (%)</td>
<td>38</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Limited joint mobility or keiropathy (%)</td>
<td>47</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Carpal Tunnel Syndrome (%)</td>
<td>21</td>
<td>20</td>
<td></td>
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<tr>
<td>Tenosynovitis (%)</td>
<td>12</td>
<td>10</td>
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</tbody>
</table>

### Materials and Methods

The diagnosis of type 2 diabetes was made/confirmed at each participating DC according to criteria defined by the ADA Standards of Medical Care in Diabetes 2017 [40]. The International Classification of Diseases, Clinical Modification (ICD-9-CM, V82.92014) was used to define T2DM diagnosis and comorbidities and/or diabetes related / unrelated complications [41]. In particular, limited joint mobility, defined as limitation in at least two anatomical areas of the dominant upper extremity was defined / diagnosed as previously described [42,43].
As part of their continuing education program and treatment agreement, at each referral to the DC all participants had been- and went on being - successfully tested for their ability to stick to the prescribed regimen and encouraged to keep their meal carbohydrate content as stable as possible, as well as, to adjust the dosage of lispro as needed according to their known insulin to carbohydrate ratio and insulin sensitivity factor.

Severity and number of hypoglycemic episodes were recorded according to patient ability to recall them, as reported in previous studies [39].

According to ADA guidelines, severe hypoglycemia was defined as a hypoglycemic episode leading to unconsciousness or requiring assistance by a third person or with a blood glucose <54 mg/dL (3.0 mmol/L) or in the 56-70mg/dL range (3.0-3.9 mmol/L); symptomatic hypoglycemia was defined as the onset of one or more of the following symptoms which resolved with the ingestion of food or sugary drinks: palpitations, tremors, sweating, shakiness, irritability, difficulty concentrating, dizziness, hunger, blurred vision, confusion, tachycardia, or difficulty moving without loss of consciousness [40].

Glycemic variability (GV) was computed according to a previously reported method as the mean standard deviation of glycemic data from a 7-14 point-per-week recording and hypoglycemic event rates were expressed as mean episodes per week [44,45].

Bone, joint or muscle disorders were present in 129 of the 190 enrolled subjects (68%). In greater detail 47% had diabetic neuropathy or limited joint mobility, 12% tenosynovitis of the long flexor muscle and 21% suffered from carpal tunnel syndrome (Table 1).

Results

As compared to baseline, at the end of the study only the HVG displayed a significantly lower rate of total hypoglycemia (p<0.01) in terms of both severe (0.2±0.1 n/week vs 6±2 n/week) and symptomatic, moderate (2 ± 1 n/week vs 10 ± 3 n/week) episodes, the same applying to fasting plasma glucose (109.1±21.1 vs 141.2±19.5 mg/dL, respectively) and mean glucose variability (140±18 vs 169±34 mg/dL, respectively) (p<0.01).

Changes in all other clinical and laboratory parameters, including HbA1c, never reached significant levels ad kept within 2% baseline values (Table 3).

The daily dosage of both glargine and lispro kept stable throughout the study but for 76% patients in the HVG, who in fact had to reduce it by about 20% within the 12-week observation period (range 14-23%).
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Satisfaction questionnaire

Main satisfaction questionnaire results are summarized (Table 4). They clearly show that 60 to 81% patients were very satisfied with different aspects of Lispro U-200 KP utilization. They especially appreciated the decrease in injected volume, local pain and effort required to complete the injection. 3 to 10% patients had no advantages at all, while 30 to 12% patients, who were mostly free from bone/joint/muscle diseases, reported only minor positive effects from using U-200 KP. Moreover, despite 30% patients being somewhat skeptical concerning the possibility for new devices and concentrated insulin preparations to improve glycemic control, 88% claimed to prefer U-200 KP in the end, versus 7% willing to go on with their original U-100 (5% remaining undecided) and when dichotomically asked which pen they would choose for the future, 90% were in favor of U-200 KP and only 10% chose their original pen.

Discussion

Our study evaluated changes occurring in main metabolic parameters after shifting from a long term U-100 lispro treatment regimen to a further 12-week utilization of the double-concentrated, half-volume U-200 lispro. As all of them had been referring long term to our DCs’s doctors, who adopt a strict best injection practice protocol consistently, all patients were using the same device and needle (4mm/32G) and followed injection guidelines, thus allowing the study to be free of any trivial method-related biases.
Being pharmacokinetic properties of U-200 and U-100 lispro superimposable, the hypothesis behind was that the halved volume injected using a specifically designed pen per se might turn into better metabolic results. A higher treatment adherence could also be expected by elderly people with musculo-skeletal defects thanks to the lower effort required to push the plunger across the full pen length.

Our results showed improved fasting blood glucose, glycemic variability and moderate/severe hypoglycemic episode rate in the HVG, whose HbA1c, despite not attaining significance, tended to decrease too. All this came with a 20% decrease in insulin requirements in 76% HVG patients. This indirectly supports our hypothesis that a lower volume makes it easier to deliver the prescribed insulin dose and prevents people from performing inefficient injections of only apparently higher drug amounts.

Moreover, the newly engineered U-200 lispro KP device might have added to that by preventing people from stopping the injection too early and thus injecting less insulin than expected. Indeed 68% patients (122 out of 180) in the HVG had hand strength/dexterity defects, which were detrimental per se on correct pen handling and on full pressure application onto the plunger and were therefore expected to prevent injections to be fully completed [27]. This might be even more convincing when considering that no dosage changes were needed in the CG, where – as seen in Table 1 - functional hand defects had the same prevalence.

Dose accuracy, ease of use and patient preference for KP, Solostar (SS) and FlexPen (FP) devices were recently investigated in 100 inexperienced diabetic subjects. Dose accuracy was evaluated through simulated injections by an applicator and a semi-automatic measuring system. Injection force was also measured by means of precision systems. KP and FP were found to be comparable to each other and more accurate than SS, being their dose error significantly lower compared to that observed for SS at any tested dose [23]. Moreover, a significantly larger amount of patients administered a satisfaction questionnaire different from ours showed to prefer KP, also for the handshake ease when injecting (68.5%, 95% CI = 62.6-73.5% - P <0.05 vs FP and SS), the "ease of use when in public" (70.2%, 95% CI = 65.3-76.8%-P <0.05 vs. FP and SS), and "global ease of use" (73.3%, 95% CI = 68.9-79.4% - p < 0.05 vs. FP and SS). The preference for KP with respect to the primary end-point "easy to push while injecting my dose" depended primarily on the fact that KP plunger was smoother and required less effort than FP
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In fact musculo-skeletal changes, especially those involving the hands are frequently observed yet mostly forgotten or inadequately investigated by physicians in people with diabetes at the time of prescription. 66% patients with type 1 diabetes have been reported to exhibit some kind of musculoskeletal defects at the hand level and insulin treated people many years after disease onset, no matter whether T1DM or T2DM patients, and to get worse results than age-matched controls in motor skills [25,26,28,29].

For the first time our questionnaire addressed patient feelings concerning the effort required to complete shots. Various experiences carried out in the past showed that pens enhance therapeutic adhesion and, as shown by Schwartz et al. [24], the latter indirectly benefits metabolic control compared to syringes. Our data are in full agreement with them, who also reported patients’ preference for KP in terms of precision, ease of use, and injection troubles. Moreover, we emphasize the fact that in our study a lower injected volume significantly improved pain at the injection site and further reduced injection thrust, thus making it easier to fully complete the injection.

This is especially important as patient’s feelings may strongly affect injection technique. Pain at the injection site, for instance, may influence time spent in injecting. Moreover, physicians and anyone else unused to repeated injections underestimate the negative role of sensation-related memory, which in fact dominates so much of patient’s attention and may therefore affect acceptance and adherence to therapy. Indeed, as recommended by all manufacturers, it is necessary to wait a few seconds (5 to 10, depending on the device and dose used) at the end of the injection to avoid loss of insulin. Nevertheless, pain at the injection site and boredom due to the lifetime routine of multiple daily injections may cause people to stop the injection process too early. Data concerning the correlation between injected liquid volume and local pain are unavailable, but a relationship between the two was reasonable [38]. With respect to that, based on our subjective patient ratings, the effort required to push the plunger down to the bottom was lower, and for the first time our study showed that a smaller injected volume associated with reduced pain/discomfort at the injection site. The association of the above with the reduced insulin doses we observed in the HVG let us hypothesize that the low volume required for a full injection allowed the whole expected insulin dose to be really provided at each shot. On the opposite, this was not the case before, when large volumes might have been only partially injected, thus reducing the amount of administered insulin, with consequent inadequate metabolic control. However, this observation was not foreseen as a possible endpoint of our study and therefore needs to be confirmed by more extensive and specifically devoted investigations.

A major limitation of our study was the short duration of real life observation and the inability to separate the effect of KP per se from that of reducing the volume of insulin lispro U-200. Nevertheless, associated KP and lispro U-200 has come up with interesting metabolic improvements.

As a final conclusion, the fact that an only 12 week observation period on U-200 insulin improved metabolic parameters by significantly reducing hypoglycemic episodes, fasting blood glucose and glycemic variability despite a lower daily insulin requirement provides objective support to subjective patient rating and checking joint functionality before insulin prescription could be adopted as a standard practice aimed at choosing the most suitable device for patient’s specific characteristics and abilities. Nevertheless a longer observation period is warranted to allow for a significant HbA1c decline, which in our hands could be only defined as a trend.

Compliance with ethical standards

Ours was a spontaneous, unconditioned study organized and supported by the AID Foundation (a non-profit organization for the study of endocrine and metabolic disorders), Naples, Italy and therefore got no commercial sponsorship.

Ethical standard

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, as revised in 2008, and was approved all the Ethics Committees of the Centers participating in the study.

Human and animal rights

All followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national).

Informed consent

Written informed consent was obtained from all participants before enrollment.
Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank the Associazione Medici Diabetologi (AMD) for its support. The components of the Italian Study Group on Injection Techniques are also acknowledged for critical reading and approval of the manuscript: Stefano De Riu, Nicoletta De Rosa, Giorgio Grassi, Gabriella Garrapa, Laura Tonutti, Katja Speese, Lia Cucco, Maria Teresa Branca, Amodio Botta.

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36. http://dx.doi.org/10.17140/DROJ-2-126


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Special issue title: Global Health Care Concerns
Handled by Editor(s): Dr. Akiko Kamimura Assistant Professor, Department of Sociology, University of Utah, U.S.

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Submitted: March 02, 2018; Accepted: March 19, 2018; Published: March 26, 2018

Global Health Care Concerns