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Dipeptidyl Peptidase-4 Inhibition in Psoriasis Patients with Diabetes: A Double-Blind Randomized Controlled Trial

Maeve Lynch^{a,b} Anna Malara^b Irene Timoney^a Tomas Ahern^c
Fatima Awdeh^a Cheryl Sweeney^b Marie Galligan^b
Sebastian Venckens^b Genevieve Kelly^a Rosalind Hughes^a
Donal O'Shea^{b,c} Peter Doran^d Brian Kirby^{a,b}

^aDepartment of Dermatology, St. Vincent's University Hospital, Dublin, Ireland; ^bSchool of Health Sciences and Charles Institute, University College Dublin, Dublin, Ireland; ^cDepartment of Endocrinology, St. Vincent's University Hospital, Dublin, Ireland; ^dClinical Research Centre, University College Dublin, Dublin, Ireland

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Dear Editor,

A role for dipeptidyl peptidase-4 (DPP-4) inhibitor therapy in the treatment of psoriasis has been suggested. DPP-4, a transmembrane glycoprotein, is expressed on keratinocytes and is upregulated in psoriasis [1]. DPP-4 inhibition suppresses keratinocyte proliferation in vitro and partially restores keratinocyte differentiation in vivo [2]. Four cases of DPP-4 inhibitor therapy improving psoriasis severity have been reported [3–5].

This randomized clinical trial assessed the effects of sitagliptin, a DPP-4 inhibitor, and gliclazide, a sulphonylurea and comparator glucose-lowering agent, on psoriasis severity, quality of life (QOL), cardiovascular disease (CVD) risk factors, and immune parameters. The inclusion criteria were: a diagnosis of chronic plaque and/or guttate psoriasis which was stable; a psoriasis area and severity index (PASI) greater than 7 at screening or baseline; and a diagnosis of type 2 diabetes mellitus (T2DM). In this 40-week, single-centre, randomized, double-blind placebo-controlled trial, people with T2DM and psoriasis were allocated randomly to receive sitagliptin or gliclazide therapy for 16 weeks, followed by sitagliptin therapy for 16 weeks, followed by a 4-week washout phase. The primary outcome measure of the trial was the change in PASI after 16 weeks of treatment. We estimated that 40 participants would need to be recruited to have 80% power to find a significant difference between groups.

Statistical analysis of trial data followed closely the analysis plan set out in the clinical trial protocol. Analysis was carried out using R version 3.3.1 (R Core Team, 2016) and SPSS Statistics version 24 (IBM, 2016). Analyses were carried out following the intention-to-

treat principle. Missing data were replaced using the last observation carried forward method.

Between April 25, 2014, and April 22, 2015, 9 participants were randomized to the sitagliptin arm and 11 to the gliclazide arm. Recruitment was halted after 20 participants had been enrolled. The recruitment period and funding had finished at that time. The baseline PASI was similar in the sitagliptin (median 9.5, IQR, 7.8–9.6) and gliclazide (median 9.4, IQR, 7.6–12) arms (Table 1). There was no significant difference between treatment arms in the change in PASI from baseline to 16 weeks (Fig. 1). The sitagliptin arm had a median reduction in PASI of 0.9 (IQR, 0.4–2.1) compared to a median reduction of 0.8 (IQR, –0.2 to 2.1) for participants treated with gliclazide ($U = 43.5$, $p = 0.648$).

From baseline to week 32, participants in the gliclazide arm (16 weeks of gliclazide and 16 weeks of sitagliptin) had a median reduction in PASI of 1.8 (IQR, 0.3–3), and those in the sitagliptin arm had a median reduction of 3 (IQR, 2–5.6, $U = 29.5$, $p = 0.128$). At 16 weeks, 50% reduction in PASI from baseline (PASI-50) was achieved by one participant per treatment arm (9.1% of the gliclazide arm, 11.1% of the sitagliptin arm). No participants achieved PASI-75 or PASI-90 after 16 weeks of treatment. At 32 weeks, 4 participants (44.4%) in the sitagliptin arm achieved PASI-50 compared to 2 (18.2%) in the gliclazide arm ($p = 0.336$). One participant (11.1%) in the sitagliptin arm achieved PASI-75 after 32 weeks, compared to 0 (0%) in the gliclazide arm ($p = 0.45$). No participant achieved PASI-90 or PASI-100 after 32 weeks of treatment.

The only statistically significant difference between treatment arms in the QOL endpoints was a small negative median change in the EuroQol 5-item questionnaire (EQ-5D) score in the gliclazide arm after 16 weeks compared to the sitagliptin arm, whose median EQ-5D value did not change ($U = 25.0$, $p = 0.047$). After 32 weeks, there was no difference in median change of EQ-5D scores between the two arms.

At 16 weeks, the change in high-sensitivity C-reactive protein (hs-CRP) concentration was lower in the sitagliptin arm than in the gliclazide arm: hs-CRP concentration did not change with sitagliptin therapy and increased with gliclazide therapy ($U = 21.0$, $p = 0.030$). At week 32, this difference was no longer significant. No other between-group differences were noted in CVD risk factors.

At week 16, the increase in active glucagon-like peptide-1 (GLP-1) and decrease in total gastric inhibitory polypeptide (GIP) after sitagliptin treatment was not significant compared to the gliclazide arm, which is interesting as sulphonylurea therapy has not demonstrated effects on GLP-1 and GIP in patients with T2DM [6]. The median insulin decreased significantly in the sitagliptin arm (median –3.91, IQR, –17.52 to 2.61) compared to the gliclazide arm (median 3.24, IQR, 1.36–7.54) at week 16 ($U = 9.0$, $p = 0.02$).

Table 1. Baseline demographics and disease characteristics

Variable	Gliclazide (<i>n</i> = 11)	Sitagliptin (<i>n</i> = 9)	Total (<i>n</i> = 20)
Age at recruitment, years	59.8 (58.2–64.3)	57.2 (54.4–61.5)	58.4 (55.7–63.4)
Caucasian ethnicity	11 (100)	9 (100)	20 (100)
Male gender	9 (81.8)	7 (77.8)	16 (80)
Duration of psoriasis, years	33.2±17.2	30±9.6	31.8±14
Smoking status			
Never	5 (45.5)	2 (22.2)	7 (35)
Current	2 (18.2)	2 (22.2)	4 (20)
Former	4 (36.4)	5 (55.6)	9 (45)
Alcohol consumed per week, units	6 (0–10)	2 (0–2)	2 (0–9)
Systolic blood pressure, mm Hg ^a	134 (126–151)	132 (129–145)	133 (129–150)
Weight, kg ^a	105.1 (78.4–118.1)	97.6 (82.8–112.2)	98.4 (82.2–115.6)
BMI, kg/m ^{2a}	36.8 (25.9–37.5)	31.1 (29.1–33.9)	33.3 (27.6–37.4)
Any psoriasis treatment at baseline	8 (72.7)	7 (77.8)	15 (75)
Any topical psoriasis therapy at baseline	7 (63.6)	7 (77.8)	14 (70)
Tar treatment at baseline	2 (18.2)	1 (11.1)	3 (15)
Corticosteroid treatment at baseline	4 (36.4)	3 (33.3)	7 (35)
Vitamin D analogue at baseline	1 (9.1)	1 (11.1)	2 (10)
Vitamin D analogue and corticosteroid	2 (18.2)	2 (22.2)	4 (20)
Coal tar 12%, salicylic acid 2%	1 (9.1)	0 (0)	1 (5)
Any biologic treatment at baseline	1 (9.1)	2 (22.2)	3 (15)
Adalimumab therapy	1 (9.1)	2 (22.2)	3 (15)
Any systemic psoriasis treatment at baseline	0 (0)	0 (0)	0 (0)
Any diabetes medication at baseline	11 (100)	7 (77.8)	18 (90)
Metformin	11 (100)	7 (77.8)	18 (90)
Insulin glargine	2 (18.2)	0 (0)	2 (10)
Insulin aspart	1 (9.1)	0 (0)	1 (5)
PASI			
Mean ± SD	9.6±2.6	8.9±1.9	9.3±2.3
Median (IQR)	9.4 (7.6–12)	9.5 (7.8–9.6)	9.4 (7.7–10.1)
BSA			
Mean ± SD	11.8±7.3	9.1±2.4	10.6±5.7
Median (IQR)	11 (4–16)	9 (8–11)	9.5 (7.3–13.5)
DLQI	7 (2–10)	3 (3–7)	6 (2.5–9.5)
HADS Anxiety	5 (1–9)	4 (3–5)	4.5 (3–6)
HADS Depression	3 (0–4)	1 (1–3)	1.5 (0–3.5)
EQ-5D index	1 (0.85–1)	1 (0.8–1)	1 (0.81–1)
HAQ-8 score	0 (0–1)	0 (0–2)	0 (0–1.5)
Visual Analogue Scale	80 (70–90)	80 (70–80)	80 (70–87.5)
Glucose, mmol/L ^b	7.6 (6.3–9.3)	7.6 (7.5–9)	7.6 (6.8–9.2)
Cholesterol, mmol/L	3.9 (3.8–4.7)	3.6 (3.5–4.3)	3.9 (3.5–4.4)
LDL cholesterol, mmol/L	2.1 (1.6–3.0)	2.1 (1.8–2.4)	2.1 (1.7–2.7)
HDL cholesterol, mmol/L	1.2 (1.1–1.3)	1.1 (1.0–1.1)	1.1 (1.0–1.2)
Triglycerides, mmol/L	1.66 (1.03–2.01)	1.64 (1.39–1.83)	1.65 (1.20–1.86)
hs-CRP, µg/mL	11.14 (4.29–19.06)	2.55 (1.16–10.58)	6.70 (1.86–15.86)
HbA _{1c} , mmol/mol	59 (51–61)	53 (52–59)	58 (51.5–60)

Continuous variables are summarized as median (IQR), if non-symmetric in distribution, and as mean (± standard deviation) otherwise. Ordinal variables are summarized as median (IQR). Categorical variables are summarized as *n* (%).

BMI, body mass index; PASI, psoriasis area and severity index; BSA, body surface area; DLQI, dermatology life quality index; HADS, hospital anxiety and depression scale; EQ-5D, EuroQol 5 item questionnaire; HAQ-8, Stanford Health Assessment Questionnaire 8-item Disability Scale; LDL, low density lipoprotein; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HbA_{1c}, glycated haemoglobin A_{1c}.

^a Data for one participant were carried forward from screening visit – not taken at baseline due to vasovagal episode.

^b Data for one participant were carried forward from screening visit – not taken at baseline due to sample not being obtained after a period of fasting.

Fig. 1. Boxplots of the change in psoriasis area and severity index (PASI) from baseline to week 16 and from baseline to week 32, by treatment arm. The black lines represent the median change in PASI from baseline values, the boxes represent the IQR, the whiskers represent the value ranges, and the dots represent outlier values (gliclazide: $n = 11$, sitagliptin: $n = 9$).

Interleukin-10 (IL-10) was not detected in the serum of any participant at weeks 16 and 32, while IL-17 was detected only in 2 participants at these time points. Interferon gamma (IFN γ) and IL-23 were also not detected in the serum of most participants. In contrast, tumour necrosis factor alpha (TNF α), resistin, leptin, and adiponectin were detected in the serum of all participants at 16 and 32 weeks, while IL-6 was detected in 70% of participants.

The median adiponectin level at 16 weeks was increased significantly in the sitagliptin arm (median 0.65, IQR, 0.00–0.85) compared to the gliclazide arm (median –0.61, IQR, –2.20 to 0.33) ($U = 22.0$, $p = 0.037$). At 32 weeks this difference was no longer significant.

The relative expression of cytokine messenger ribonucleic acid (mRNA) transcripts in skin biopsies was measured in 6 participants, 3 from each treatment arm. The mRNAs of the cytokines showed similar expression in skin biopsies of the participants. The decrease in cutaneous DPP-4 expression at week 32 was significantly lower in the sitagliptin arm compared to the gliclazide arm ($U = 0.0$, $p = 0.05$).

No deaths occurred during the study period. No participant discontinued study participation due to a treatment-related adverse event. Adverse events occurred in 91% ($n = 10$) of participants in the gliclazide arm and 67% ($n = 6$) in the sitagliptin arm which was due mainly to a difference between hypoglycaemia incidence in the sitagliptin arm ($n = 1$, 11%) and the gliclazide arm ($n = 9$, 82%). There were no treatment-related serious adverse events.

In this study of 20 patients, sitagliptin therapy did not significantly improve psoriasis severity compared to gliclazide therapy at 16 weeks. The fact that this study was underpowered precludes further speculation on sitagliptin efficacy in psoriasis. There were no safety issues with sitagliptin during this study. There were no significant differences in serum cytokines or hormones apart from insulin and adiponectin between the two arms. The marginal impact of therapies on QOL measures may, in part, be due to a floor effect [7]. Most patients had minimal impairment of QOL at baseline – baseline median DLQI of 6

(2.5–9.5) and EQ-5D score of 1 (0.81–1) – and therefore it is difficult to demonstrate a difference even if an improvement has occurred.

The majority of the participants (70%) in this study were receiving topical psoriasis therapies during the trial. Three participants (15%) were being treated with the biologic agent adalimumab for their psoriasis. These therapies may have impacted on the change in psoriasis severity during the study period, although no changes were made to these treatments during the study.

The effects of DPP-4 inhibition on the immune system are not well known. In this study at week 16, an increase in hs-CRP concentration was noted in the gliclazide arm which was significantly different to the change in the sitagliptin arm ($U = 21.0$, $p = 0.03$); this difference did not correlate with a significant change in psoriasis severity between the two arms.

In conclusion, sitagliptin therapy resulted in no change in psoriasis severity when compared to gliclazide therapy in a small group of people with both psoriasis and T2DM.

Key Message

There were no statistically significant differences between sitagliptin therapy and gliclazide therapy on psoriasis severity.

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Statement of Ethics

All participants attested in writing to giving informed consent to participate in the trial after receiving oral and written information. The trial was approved by The Health Products Regulatory Authority of Ireland (HPRA) and by the St. Vincent's University Hospital Ethics and Medical Research Committee.

Disclosure Statement

B.K. has acted as an advisory board member for Pfizer, AbbVie, Novartis, Celgene, Janssen, Leo, Almirall, and Lilly. He has received research support or been a primary investigator for clinical trials with AbbVie, Pfizer, Merck & Co., and Novartis. He has also acted as a consultant to Merck & Co., Pfizer, Janssen, AbbVie, Novartis, Celgene, Almirall, Lilly, and Leo, and has received honoraria from Janssen, Pfizer, AbbVie, Novartis, Celgene, Almirall, Lilly, and Leo. M.L. has been in receipt of an unrestricted research grant from Merck & Co. and has acted as an advisory board member for Novartis. All other authors report no conflicts of interest.

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Author Contributions

M.L., T.A., D.O'S., P.D., and B.K. made substantial contributions to the conception and design of the study and B.K. is the principal investigator for the trial. M.L., B.K., I.T., F.A., A.M., C.S., G.K., and R.H. were involved in data acquisition. M.L., B.K., A.M., C.S., M.G., and S.V. were involved in data analysis and interpretation of data. M.L. and B.K. were involved in drafting the article. All authors revised the article critically.

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