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ABOUT COVER

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Dipeptidyl peptidase-4 inhibitor-induced autoimmune diseases: Current evidence

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Abstract

Dipeptidyl peptidase-4 inhibitors (DPP-4i) have an important place in the management of type 2 diabetes. The DPP-4 enzyme is ubiquitously distributed throughout the human body and has multiple substrates through which it regulates several important physiological functions. DPP-4 regulates several immune functions, including T-cell activation, macrophage function, and secretion of cytokines. Studies have reported an increase in autoimmune diseases like bullous pemphigoid, inflammatory bowel disease, and arthritis with DPP-4i use. The relationship of DPP-4i and autoimmune diseases is a complex one and warrants further research into the effect of DPP-4 inhibition on the immune system to understand the pathogenesis more clearly. Whether a particular cluster of autoimmune diseases is associated with DPP-4i use remains an important contentious issue. Nevertheless, a heightened awareness from the clinicians is required to identify and treat any such diseases. Through this review, we explore the clinical and pathophysiological characteristics of this association in light of recent evidence.

Key Words: Autoimmune disease; Bullous pemphigoid; Diabetes; Dipeptidyl peptidase-4 inhibitors; Gliptins; Inflammation

Core Tip: Dipeptidyl peptidase-4 (DPP-4) has an important role in the function of the

immune system. DPP-4 inhibitors are an important drug class for the management of type 2 diabetes mellitus. This group of drugs can have a diverse effect on immune modulation. Recently, certain autoimmune diseases are described with the use of DPP-4 inhibitors, particularly bullous pemphigoid. Clinicians should be aware of this association and take appropriate action if such an adverse event takes place.

INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4i), also known as gliptins, are being increasingly used as a second-line add-on therapy in diabetes mellitus[1]. They have certain advantages as an oral hypoglycaemic agent like weight neutrality, lesser risk of hypoglycaemia, and insulin independent mechanism of action compared to other medications like sulfonylureas[2]. Sitagliptin, saxagliptin, alogliptin, and linagliptin are Food and Drug Administration (FDA) approved DPP-4is[3]. However, other DPP-4is like teneligliptin, anagliptin, and vildagliptin are also in use in different countries across the globe.

DPP-4, also known as cluster of differentiation 26 (CD26) molecule, is expressed in many tissues and known for its role in diverse physiological functions of the human body. The interaction of the DPP-4 molecule and the immune system is complex. This includes regulation of a various subset of the immune cells including T cells and antigen presenting cells. Therefore, DPP-4i has the potential to modulate various immunological functions. Indeed, the therapeutic role of DPP-4i has been studied in autoimmune diseases (AD) like type 1 diabetes mellitus[4], latent autoimmune diabetes of the adult[5], acute graft *vs* host disease[6], autoimmune encephalomyelitis [7], and multiple sclerosis[8]. However, in recent times several studies have shown an increased risk of certain AD like bullous pemphigoid (BP) among DPP-4i users. Thus, through this review, we summarise the currently available literature in the field of DPP-4i induced AD.

SEARCH STRATEGY

The keywords and combination of keywords for literature search are summarised in the Table 1. The initial literature search was carried out by three authors (AR, NN, and CM) independently in PubMed. The search was performed from the date of inception until January 15, 2021 to find relevant articles. The studies available in the English language were selected for this review. Relevant references in the individual articles were also scrutinised for their suitability and included in this review if found to be appropriate. The studies that evaluated the development of AD in patients treated with DPP-4i were selected by the authors (JS, SK, and DN) and were included in this review. We have given preferences to the most recent studies published in the last 5 years.

THE INTERFACE BETWEEN IMMUNE SYSTEM AND DPP-4 ENZYME

DPP-4 is an enzyme that has a ubiquitous presence throughout the human body. The most important metabolic function is to cleave various gut peptides known as 'incretin hormones' like glucagon-like peptide-1, glucose-dependent insulinotropic peptide, and neuropeptide Y[9]. Incretins have several metabolic benefits like enhanced insulin secretion from the pancreatic beta cells and thus help in controlling blood glucose in subjects with diabetes[10]. DPP-4i prolongs the half-life of different incretins by inhibiting intestinal DPP-4 enzyme activity.

Table 1 List of the keywords used for literature search	
No.	
1	Dipeptidyl peptidase 4 inhibitor
2	DPP-4 inhibitor
3	Gliptins
4	'Autoimmune disease'
5	[1] and [4]
6	[2] and [4]
7	[3] and [4]
8	[2] and [3] and [4]
9	Inflammatory bowel disease
10	[1] and [9]
11	Arthritis
12	Arthralgia
13	'Rheumatoid arthritis'
14	[1] and [11]
15	[1] and [12]
16	[1] and [13]

DPP-4: Dipeptidyl peptidase-4.

The details of the role of DPP-4/CD26 in immune system is beyond the scope of this review and many elegant reviews are already there in this area[11,12]. The CD26 molecule, also known as the 'moonlight protein' is a cell surface protein having significant DPP-4 activity. DPP-4 is expressed in several cell lines involved in the pathway of immune regulation. These include T helper cells type 17 (Th17), natural killer cells, activated B cells, macrophages, and myeloid cells[12]. DPP-4 is a transmembrane protein having three parts: a small intracellular part, a transmembrane part carrying the DPP-4 activity, and a large extracellular part[12]. There is also a soluble form of DPP-4 (sDPP-4) that carries a significant amount of enzyme catalytic activity[9]. Recent evidence suggests that circulating lymphocytes are an important source of the sDPP-4[13]. sDPP-4 is used as a biomarker of several diseases and a reduced serum level has been described in rheumatoid arthritis (RA), systemic lupus erythematosus, and psoriasis[12,14]. An elevated sDPP-4 has been shown in type 1 diabetes suggesting its role in the pathogenesis[15].

DPP-4 promotes activation and proliferation of both T cells (Th1, Th17, and regulatory T cells)[16,17], and macrophages[18]. It also has a role in the immuno-globulin synthesis regulation like isotype switching of B cells[19]. Moreover, evidence also suggests that DPP-4 significantly modulates secretion of different cytokines and chemokines, thus regulating tissue response to injury[20,21]. DPP-4i increases stromal derived factor-1 (or CXCL12) levels, which has several pleiotropic effects[22], *e.g.*, beneficial effects in ischemic myocardium[23], diabetic nephropathy[24] and stroke [25]. Interestingly, a recent study demonstrated a decrease in certain chemokines (CCL11/Eotaxin, CCL22/MDC, and CXCL10/IP-10) following a mixed meal test after 6 mo of teneligliptin treatment in diabetes patients[26]. Nevertheless, the exact role of different cytokines/chemokines cleaved by the DPP-4 enzyme in immune regulation remains an unexplored area[27].

Several experimental studies have shown that DPP-4i suppresses various markers of inflammation[28] and/or fibrosis[29] and thus is regarded as an attractive therapeutic option in AD. Several animal research studies have shown the beneficial effects of DPP-4i in obesity-related inflammation[30], hepatic fibrosis[31], myocarditis[32], and diabetic nephropathy[25,26,33], as well as chemotherapy induced renal injury[34] through its immune-modulatory action. Earlier studies also showed the potential beneficial role of DPP-4i in different inflammatory central nervous system disorders, including multiple sclerosis[7,35]. However, several other studies have reported an

increased risk of a few specific AD with DPP-4i use, which are described below.

DPP-4I USE AND RISK OF OVERALL AD

In recent times, several studies have evaluated the association of different DPP-4i with overall AD. However, these studies are limited by the fact that most of them are either retrospective or cross-sectional in nature, and few studies assessed the full autoimmune spectrum. Kridin *et al*[36] from Israel reported that the prevalence of 3 AD (Crohn's disease, psoriasis and Hashimoto's thyroiditis) out of nearly 15 AD was significantly higher in the DPP-4i-treated group as compared to age, gender, and ethnicity-matched diabetes control subjects. This study suggested that a cluster of AD might be associated with DPP-4i treatment. On the other hand, a Japanese study based on the analysis of the adverse drug reaction database showed an increased risk of overall AD in the older age group (> 60 years)[37]. However, a recent population-based study[38] performed in Asian people found that DPP-4i treatment was significantly associated with a reduction in the prevalence of overall AD [adjusted hazard ratio (aHR): 0.56 (95% confidence interval (CI): 0.53–0.60; $P < 0.001$)]. The AD included RA, systemic lupus erythematosus, inflammatory bowel disease (IBD), Sjogren's syndrome, psoriasis, and ankylosing spondylitis. Similar results indicating a lower risk of overall AD had been demonstrated by a few other studies[39,40]. Chen *et al*[38] also showed that the risk of AD was significantly lower in the younger population. This finding signifies the importance of age as an important determining factor of autoimmunity. Clinicians must be vigilant about the risk of different AD in DPP-4i treated patients as summarised in Table 2.

DPP-4I USE AND RISK OF BP

BP is the commonest skin AD associated with DPP-4i use, as described in the literature. However, pemphigus vulgaris has been reported rarely[41] in patients using DPP-4i. BP is a blistering skin condition that occurs commonly in the elderly population. It is an AD characterised by the presence of circulating autoantibodies directed against BP180 and BP230 autoantigens in basal keratinocytes. BP is caused by several drugs and carries a significant risk of mortality[42]. The recent addition to the list of the drugs is DPP-4i. Since 2011, many case reports[43-45] and case series[46-48] have reported the association between the use of DPP-4i and development of BP. In recent times, both observational and retrospective studies[49-54] and adverse drug event-based registries[55,56] have also shown this association (Tables 3 and 4).

Estimating the risk of BP with DPP-4i use

After the initial information obtained from the case reports and case series, adverse drug reaction-based databases have increasingly reported the association of BP with the use of DPP-4i[49,57-59]. Similarly, nation-wide population-based studies[50,60,61] also strengthened this association further as summarised in Table 3. However, it is important to note that most of the pharmacovigilance and adverse database studies have mentioned reporting odds ratio (ROR) to gather early signals of the association between DPP-4i use and BP. However, ROR neither allows to establish any association nor proves causality[62]. Moreover, a few meta-analyses[63,64] tried to sum-up the available data. DPP-4i use in diabetes is associated with both de novo development of BP as well as exacerbation of the already existing BP[65]. It is also important to note that studies have reported increasing diabetes prevalence in BP patients[66], so one should be cautious while prescribing DPP-4i in these patients.

How much is the risk? The answer is not a straightforward one. There is definite evidence that increased risk of BP is a class effect of DPP-4i use, and it varies from molecule to molecule. Studies have reported a 2-3 times risk (as reported by aHR) of developing BP in diabetes patients receiving DPP-4i (Tables 3 and 4). The meta-analysis performed by Phan *et al*[64] on five case-control studies reported overall OR of 2.13 (95%CI: 1.59-2.86) for developing BP in DPP-4i users. Furthermore, a recent meta-analysis including randomized controlled trials (RCTs) as performed by Silverii *et al*[63] reported a Mantel-Haenszel OR of 4.44 (95%CI: 1.31-15.00) for overall DPP-4i use and development of BP. However, the included number of BP cases was low (*n* = 17), and most of the data came from linagliptin trials, thus drawing conclusions about other DPP-4is was not possible from this study. It also underscores the importance of

Table 2 Summary of the studies that assessed risk of overall autoimmune diseases in dipeptidyl peptidase-4 inhibitor users

Ref.	Population	Study design	Composite outcome	Individual autoimmune disease outcome
Kridin *et al*[36], 2018	T2DM patients receiving DPP-4i (*n* = 283) *vs* matched controls (*n* = 5660)	Cross-sectional retrospective study using patient database	OR 1.44 (95%CI: 1.06–1.96) for any disease from the cluster of AD (Crohn's disease, psoriasis, Hashimoto's thyroiditis, MS, ulcerative colitis)	Crohn's disease OR 3.56 (95%CI: 1.04–12.21). Psoriasis OR 2.12 (95%CI: 0.99–4.66). Hashimoto's thyroiditis OR 1.38 (95%CI: 1.00–1.91). No difference in the following ADs: Addison's disease, Arthropathy, Celiac disease, Idiopathic thrombocytopenic Purpura, Myasthenia gravis, Pernicious anaemia, RA, Sarcoidosis, Scleroderma, SLE
Noguchi *et al*[37], 2019	Diabetes patients receiving DPP-4i and other antidiabetic drugs (*n* = 38887)	Adverse Drug Event Report database analysis	PRR 4.09 for overall autoimmune disease	Increased risk was noted in the following AD: RA, pemphigoid, autoimmune pancreatitis, and polymyalgia rheumatica
Chen *et al* [38], 2020	T2DM patients (age ≥ 20 yr) receiving DPP-4i *vs* non-DPP-4i medications (*n* = 387099 in each group)	Retrospective cohort study using insurance claim data	HR 0.56 (95%CI: 0.53–0.60) for overall AD like RA, SLE, IBD, Sjogren syndrome, psoriasis and ankylosing spondylitis	RA: HR 0.56 (95%CI: 0.46–0.68). Psoriasis: HR 0.56 (95%CI: 0.52–0.61). Ankylosing spondylitis: HR 0.56 (95%CI: 0.50–0.63). SLE: HR 0.55 (95%CI: 0.35–0.88). IBD: HR 0.66 (95%CI: 0.11–3.95). Sjogren syndrome: HR 0.58 (95%CI: 0.46–0.75)
Kim *et al* [39], 2015	T2DM patients (age ≥ 40 yr) started on DPP-4i as a part of combination therapy (*n* = 73928) *vs* non-DPP-4i combination therapy (*n* = 163062)	Cohort study using insurance claim data	HR 0.68 (95%CI: 0.52-0.89) for AD like RA, SLE, psoriasis, psoriatic arthritis, MS and IBD	RA: HR 0.66, (95%CI: 0.44-0.99). Other AD (excluding RA): HR 0.73 (95%CI: 0.51-1.03)
Seong *et al* [40], 2019	New T2DM patients (age ≥ 18 yr) using DPP-4i (*n* = 497619) or non-DPP-4i (*n* = 643165) oral combination therapy	Active comparator new-user cohort study	aHR 0.82 (95%CI: 0.68–0.99) for AD like RA, IBD, MS and SLE	RA: aHR 0.67 (95%CI: 0.49-0.92). IBD: aHR 0.81 (95%CI: 0.61-1.08). SLE + MS: aHR 0.67 (95%CI: 0.37-1.19)

AD: Autoimmune disease; aHR: Adjusted hazard ratio; CI: Confidence interval; DPP-4i: Dipeptidyl peptidase-4 inhibitor; HR: Hazard ratio; IBD: Inflammatory bowel disease; MS: Multiple sclerosis; OR: Odds ratio; PRR: Proportional reporting ratio; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; T2DM: Type 2 diabetes mellitus.

systematic reporting of AD including BP as an adverse event in large clinical trials involving other DPP-4is.

Individual DPP-4i and risk of BP

Almost all of the DPP-4is are associated with the development of BP. However, vildagliptin is the most commonly implicated drug in the published literature. Both pharmacovigilance[64] and observational studies[57,67,68] reported vildagliptin use as a risk factor for development of BP with a OR varying from 1.81 to 10.40. Moreover, the meta-analysis by Phan *et al*[64] concluded that vildagliptin has the highest risk (OR 5.08) followed by linagliptin (OR 2.87). But sitagliptin was not associated with BP (OR 1.29, 95%CI: 0.79-2.08). Linagliptin had a similar propensity (HR 4.90, 95%CI: 2.68–8.96) to cause BP as vildagliptin (HR 4.56, 95%CI: 1.42–14.64) in a recently published study[57]. The conclusion of a recently conducted meta-analysis[63] also revealed an increased risk of BP in linagliptin-treated patients (Mantel-Haenszel-OR 4.69, 95%CI: 1.09-20.22). Additionally, few reports have also revealed teneligliptin[58, 69] and saxagliptin[46,56-58,70] induced BP. However, there is a possibility of reporting bias present since BP is not systematically reported in large clinical trials involving various DPP-4i.

Risk factors for the development of DPP-4i induced BP

Older age is one of the important risk factors, and most of the studies have reported the mean age of subjects with DPP-4i induced BP > 70-75 years (Table 5). But Lee *et al* [57] has shown that the risk was similar between patients with more than or less than 75 years of age. The second important risk factor is male gender. Kridin and Bergman [71] reported a higher risk in males compared to females (OR 4.46 *vs* 1.88). In the same way, other studies also reported a male predilection[72]. On the contrary, Varpuluoma *et al*[60] reported that females are more likely to develop DPP-4i induced BP. Phan *et al* [64] in their pooled meta-analysis found that both genders are susceptible to develop BP with higher propensity in males (OR 2.35 *vs* 1.88). The third risk factor is the DPP-4i with less selective DPP-4 enzyme inhibition like vildagliptin. The fourth is a recently discovered association of specific human leucocyte antigen (HLA) HLA-DQB1*03:01 with DPP-4i induced BP in Japanese population[73]. However, Lindgren *et al*[74] did

Table 3 Summary of the pharmacovigilance and population-based studies reporting dipeptidyl peptidase-4 inhibitor induced bullous pemphigoid

Ref.	Country	Population	Pooled odds ratio	Individual DPP-4i	Remarks
Reolid *et al*[55], 2020	Spanish Pharmacovigilance System	Overall reported adverse events	NA	ROR: linagliptin 69.42 (95%CI: 21.17–227.57), saxagliptin 46.45 (6.26-344.25), vildagliptin 123.38 (95%CI: 68.72–221.15), sitagliptin 12.42 (95%CI: 3.89–39.63)	Vildagliptin was the DPP-4i that most frequently induced BP
García *et al*[56], 2016	European pharmacovigilance database	Overall reported adverse events	NA	PRR: Vildagliptin 85.98 (95%CI: 70.98–104.15), sitagliptin 4.55 (95%CI: 3.32–6.24), saxagliptin 8.36 (95%CI: 3.14–22.28), linagliptin 24.32 (95%CI: 14.11–41.92)	Alogliptin was not associated with development of BP
Lee *et al*[57], 2019	Korea (Retrospective, nationwide, population-based, case-control study)	670 patients with diabetes with BP and 670 control patients with only diabetes	aOR, 1.58 (95%CI: 1.25-2.00)	Vildagliptin aOR 1.81 (95%CI: 1.31-2.50), sitagliptin aOR, 1.70 (95%CI: 1.19-2.43), linagliptin aOR 1.64 (95%CI: 1.15-2.33)	Male gender was associated with higher risk of development of BP
Carnovale *et al* [58], 2019	World Health Organization global Individual Case Safety Reports database	Overall reported adverse events	ROR 179.48 (95%CI: 166.41–193.58)	Teneligliptin 975.04 (95%CI: 801.70–1185.87), sitagliptin 46.52 (95%CI: 40.57–53.36), vildagliptin 399.70 (95%CI: 362.26–441.02), linagliptin 143.23 (95%CI: 122.60–167.33)	The highest ROR was found for teneligliptin
Béné *et al*[59], 2016	French Pharmacovigilance Database	Among 1297 spontaneous ADR reports, 42 were DPP-4i induced BP	ROR 67.5 (95%CI: 47.1-96.9)	Vildagliptin ROR 225.3 (95%CI: 148.9-340.9), sitagliptin ROR 17.0 (95%CI: 8.9-32.5), saxagliptin ROR 16.5 (95%CI: 2.3-119.1)	Vildagliptin had higher ROR
Varpuluoma *et al* [60], 2018	Finland (Nationwide Registry Study)	3397 BP cases and 12941 controls	aOR 2.13 (95%CI: 1.51–3.00)	aOR vildagliptin 8.66 (95%CI: 4.06-18.50), aOR sitagliptin 1.36 (95%CI: 0.93-1.99)	A significantly increased risk of BP after the use of vildagliptin
Hung *et al*[61], 2020	Taiwan (Nationwide, population-based, cohort study)	6340 patients with DM on DPP-4i and 25360 DM patients without DPP-4i	aHR 2.382 (95%CI: 1.163-4.883)	Vildagliptin aHR, 2.849 (95%CI: 1.893-4.215), saxagliptin aHR, 2.657 (95%CI: 1.770-3.934), sitagliptin aHR, 2.585 (95%CI: 1.723-3.829), linagliptin aHR, 2.360 (95%CI: 1.567-3.477), alogliptin aHR, 1.450 (95%CI: 0.965–2.152)	Vildagliptin was significantly associated with an increased risk of BP, and alogliptin was not associated with development of BP
Arai *et al*[49], 2018	Japanese Adverse Drug Event Report database	392 BP cases in DPP-4i user and 12811 without BP as control	ROR 87.56 (95%CI: 72.61–105.59)	ROR: alogliptin 8.02 (95%CI: 4.87–13.22), anagliptin 10.84 (95%CI: 3.46–33.96), sitagliptin 12.59 (95%CI: 9.86–16.06), trelagliptin 13.77 (95%CI: 3.40–55.85), saxagliptin 15.85 (95%CI: 5.87–42.79), linagliptin 28.96 (95%CI: 21.38–39.23), omarigliptin 43.79 (95%CI: 5.85–327.70), teneligliptin 58.52 (95%CI: 42.75–80.10), vildagliptin 105.33 (95%CI: 88.54–125.30)	The highest ROR was found with vildagliptin
MolinaGuarneros *et al*[70], 2020	Spain (pharmacovigilance data)	Case/non-case analysis (1998 DPP-4i induced ADR where 45 were DPP-4i induced BP)	ROR 70.0 (47.1–104.1)	Vildagliptin 113.9 (95%CI: 73.4–177), linagliptin 55.2 (95%CI: 28.2–108.0), sitagliptin 9.1 (95%CI: 3.7–22.6), saxagliptin 27.4 (95%CI: 3.7–200.1)	Highest risk of BP with vildagliptin
Douros *et al*[80], 2019	United Kingdom Clinical Practice Research Datalink	Cohort study among 168774 patients started on antidiabetic drugs	HR 2.21 (95%CI: 1.45-3.38)	Linagliptin HR 4.90 (95%CI: 2.68–8.96), vildagliptin HR 4.56 (95%CI: 1.42–14.64), saxagliptin HR 2.16 (95%CI: 0.86–5.46), sitagliptin HR 1.42 (95%CI: 0.79–2.53)	HRs for development of BP gradually increased with longer durations of DPP-4i use

ADR: Adverse drug reaction; aHR: Adjusted hazard ratio; aOR: Adjusted odds ratio; BP: Bullous pemphigoid; CI: Confidence interval; DPP-4i: Dipeptidyl peptidase-4 inhibitor; DM: Diabetes mellitus; NA: Not available; PRR: Proportional reporting ratio; ROR: Reporting odds ratio.

not find a similar association in Caucasians. The other possible associated risk factors are mentioned in Table 5[75-77].

Table 4 Clinical characteristics of case-control studies reporting dipeptidyl peptidase-4 inhibitor-induced bullous pemphigoid

Ref.	Type of the study	Population	Effect of gender	Latency period	Age	Outcome
Plaquevent *et al*[50], 2019	Multicentre case-control study	Out of 1787 patients with BP, 108 subjects were gliptin users. Comparison with a large general population data base	NA	14.8 mo (interquartile range 6.0-26.7 mo)	77.9 ± 9.3 yr	No difference in outcome between gliptin withdrawal *vs* continued groups
Schaffer *et al* [51], 2017	Retrospective case-control study	Patients with diabetes and BP (*n* = 23) compared with patients with only diabetes (*n* = 170)	NA	Range: 5-48 mo	77.6 yr	Favourable outcome after gliptin withdrawal; however topical and systemic therapy were required in most of the cases
Béné *et al*[59], 2016	Case/non case analysis from database	Patients with BP (*n* = 150) compared with other spontaneous adverse drug reactions	NA	10 mo (range 8 d-37 mo)	74 yr (range 45-91)	Favourable outcome in patients when DPP-4is were discontinued. Median time to improvement was 10 d (interquartile range : 5-15 d)
Benzaquen *et al*[68], 2018	Retrospective case-control study with 1:2 design	Patients with diabetes and BP (*n* = 61) compared with patients with only diabetes (*n* = 122)	Male aOR 4.36 (95%CI: 1.38-13.83), females 1.64 (95%CI: 0.53-5.11)	Median 8.2 mo (range 10 d to 3 yr)	79.1 ± 7.0 yr	Favourable outcome when DPP-4is were discontinued
Kridin and Bergman[71], 2018	Retrospective case-control study	Diabetes patients with BP (*n* = 82) *vs* age and gender matched control population with only diabetes (*n* = 328)	Male OR 4.46 (95%CI: 2.11-9.40), female OR 1.88 (95%CI: 0.92-3.86)	Median 10.4 mo (range 1.0-26.5 mo)	79.1 ± 9.1 yr	Favourable outcome in gliptin withdrawal group

aOR: Adjusted odds ratio; BP: Bullous pemphigoid; CI: Confidence interval; DPP-4is: Dipeptidyl peptidase-4 inhibitors; NA: Not available; OR: Odds ratio.

Table 5 Emerging risk factors for development of dipeptidyl peptidase-4 inhibitor-induced bullous pemphigoid

Risk factors	Possible risk/trigger factor[1]
Older age (> 70 yr of age)[57,59,68]	Longer duration of DPP-4i use[64]
Male gender[64,71]	Patients with dementia[53,54]
Specific HLA like HLA-DQB1*03:01 (In Japanese population)[73]	Concomitant use of spironolactone[53]
Certain DPP-4i[63,64] (*i.e.* vildagliptin, linagliptin)[2]	Chronic kidney disease[54,77] and haemodialysis[76]
	Thermal Burn[75]

[1]Based on small studies and case reports.

[2]High likelihood of modifications of the list as new data emerges. DPP-4i: Dipeptidyl peptidase-4 inhibitor; HLA: Human leucocyte antigen.

Clinical course of DPP-4i induced BP

Latency period: The reported range of latency period for the development of DPP-4i induced BP varies widely. It ranges from 8 d to 4 years[59,63,64,78] (Table 4). A very recent case series[79] reported a median latency period of 64 mo (range 20-128 mo); however, such an association is deemed as 'possible,' and causality is difficult to establish in such cases. Douros *et al*[80] showed that the risk of development of BP increases with longer duration of use of DPP-4i, and the peak reaches around 20 mo after exposure to DPP-4i. Molina-Guarneros *et al*[70] reported a variable latency period between different DPP-4i, where linagliptin has the shortest (3.5 mo) and sitagliptin has the longest (12 mo) latency period.

Clinical characteristics of DPP-4i induced BP: As more evidence is emerging, the clinical characteristics of DPP-4i induced BP are becoming clearer[81,82]. Moreover, studies have started differentiating this disease from the more common classical BP. The BP lesions in DPP-4i treated patients are described as a predominantly 'non-inflammatory' phenotype and often exhibit lesser erythema when compared to the classical BP lesions[83,84]. Furthermore, a study performed in an Israeli cohort reported that DPP-4i induced BP had more extensive involvement and a predominant distribution of the lesion in the cephalic and truncal region of the body when

compared with other non-DPP-4i associated variants of BP[85]. A predominant mucosal involvement in DPP-4i induced BP was also reported by Kridin and Bergman [71]. But this finding was not duplicated in other studies[64,72,73,86,87]. Another interesting feature of DPP-4i associated BP is lower peripheral eosinophil count[71] as well as less eosinophilic infiltrate in the skin lesion[83,88]. But Bellinato *et al*[89] did not find any such difference. These conflicting results warrant further research to look into this area, preferably in long-term follow-up studies.

Is DPP-4i induced BP a distinct immunological phenomenon?: BP is an immuno-logical disease characterized by the development of autoimmunity against the BP180 and BP230 protein, both of which are hemi-desmosomal protein present in the dermo-epidermal junction[81]. BP180 is also known as collagen XVII. The principal autoantibody involved in the pathogenesis of the classic variant of BP is the one that acts against the extracellular non-collagenous part named the NC16A domain[90]. However, there is some evidence that DPP-4i induced BP has a different autoantibody profile compared to its classic counterpart. In an earlier report, Izumi *et al*[83] reported that a significant proportion of the DPP-4i induced BP patients had immunoglobulin G autoantibody against epitope other than the known NC16A region. Moreover, patients with non-NC16A antibodies had less inflammation and erythema, which is often-described in patients with DPP-4i induced BP. A lesser prevalence of anti-NC16A antibody in DPP-4i induced BP was also described by Horikawa *et al*[84]. Interestingly, they reported that the majority of the anti-NC16A antibody-negative patients had antibody against the full-length BP180 antigen. Another study from Japan also described a similar finding[52]. However, this specific antibody profile that could differentiate DPP-4i induced BP from the classical variety was not demonstrated in studies performed in the European population[87,89,91]. Further research is needed in this area to better characterize the role of certain autoantibodies in the pathogenesis and to use them as markers for DPP-4i induced BP.

Effect of DPP-4i withdrawal on the outcome of BP: It is expected that DPP-4i withdrawal will lead to an improvement in BP. Studies had reported a favourable outcome when DPP-4i was withdrawn after the diagnosis of BP[59,68,71]. Moreover, mortality remained significant in few studies if DPP-4i was not withdrawn[68,71]. The outcome had been measured in terms of achievement of complete or partial remission. However, even after DPP-4i withdrawal, some patients may require topical or systemic glucocorticoids depending upon the severity of the lesions[59,68,71]. Contrarily, one study found no difference in the outcome of BP lesions irrespective of the withdrawal status of DPP-4i[50]. In fact, the effect of DPP-4i withdrawal in the natural history of BP is often complicated by the fact that concomitant topical and/or systemic glucocorticoids are already being used as a therapy of BP. Despite withdrawal of DPP-4i, BP may not remit fully and require glucocorticoid therapy. Therefore, DPP-4i might play a role of aggravator of BP rather than independently inducing BP in some cases. The time taken for the improvement of BP lesions also varies in different studies. One study reported a median time for improvement of 10 d after drug withdrawal[59], whereas other studies reported months to improve[68]. Re-challenge or replacement with another DPP-4i carries a high risk of relapse of BP[59, 68] and thus preferably should be avoided. A very recent retrospective study reported that linagliptin induced BP might be difficult to treat, and it requires a higher dosage of systemic glucocorticoid compared to vildagliptin-induced BP[85].

DPP-4I USE AND RISK OF IBD

IBD is a chronic, relapsing, intestinal inflammatory condition in which various genetic, immunological, and environmental factors play a critical role. Earlier, the experimental studies showed a beneficial effect of DPP-4i use in animal models of colitis[92]. Thus, it was suggested that DPP-4i can be used as a potential therapeutic agent in IBD[8]. Studies have shown that DPP-4 levels in the plasma as well as in tissue are decreased in IBD patients compared to healthy controls[93], and the lower DPP-4 level correlates with higher disease activity and serum inflammatory markers like C-reactive proteins [94,95]. Thus DPP-4i use is expected to have a potential impact on the immunopatho-genesis of IBD. DPP-4i can also have an indirect effect on IBD by increasing the levels of different incretin hormones like glucagon-like peptide-1, glucagon-like peptide-2, and vaso-active intestinal peptide[93], though a direct effect of the DPP-4 molecule is still a possibility[96]. The clinical data are quite contrary to this basic science research.

In a population-based cohort study by Abrahami *et al*[97] in the United Kingdom, it was shown that the use of DPP-4i was associated with an increased risk of IBD with an HR of 1.75 (95%CI: 1.22- 2.49; the estimated risk was 53.4 *vs* 34.5 *per* 100000 person years in DPP-4i users *vs* non-users). The maximum risk was seen after 3-4 years of DPP-4i use (HR 2.90, 95%CI: 1.31-6.41), and the risk declined thereafter. Another population-based study by Kridin *et al*[36] showed a three and half times increased risk of Crohn's disease in DPP-4i users (OR 3.56; 95%CI: 1.04-12.21, *P* = 0.031). Wang *et al*[98] also demonstrated the increased risk of IBD in DPP-4i users while assessing the FDA's Adverse Event Reporting System database. Radel *et al*[99] performed a meta-analysis that included 16 studies (including major cardiovascular outcome trials of DPP-4i like EXAMINE, SAVOR-TIMI, and TECOS trial; *n* = 198404) and found a significantly increased relative risk (RR) 3.01 (95%CI: 2.30-3.93) of IBD using a fixed-effects model. However, the most important limitation of the analysis was that the data was driven mainly by the study of Abrahami *et al*[97]. Moreover, a random effect analysis did not reveal any elevation in the IBD risk among DPP-4i users, and the duration of most of the trials included in the analysis were less than 4 years.

On the other hand, another meta-analysis (included 13 RCTs) performed by Li *et al* [100] did not show any increase in the IBD risk among the DPP-4i users as compared to control population (RR 1.01, 95%CI: 0.30-3.41). The reported heterogeneity of the studies was low(l^2 = 0%). However, the mean follow-up period was only 1.5 years. Wang *et al*[101] also evaluated this association in the real-world setting using the insurance databases and compared the risk of IBD between DPP-4i with sulfonylurea and thiazolidinedione users. During a median duration of 1.09–1.69 years, DPP-4i was not found to be associated with a risk of IBD. The population-based studies that evaluated the overall AD composite outcomes also did not find increased risk of IBD [39,40].

To summarise, the data suggest a modest association of DPP-4i use and the development of IBD in studies that specifically looked for it, whereas pooled analysis of the RCT data failed to confirm this finding. Since the duration of the studies including many of the RCTs are short, a continued and watchful observation is required, particularly during the post-marketing surveillance. Future RCTs on DPP-4i should also systematically report development of IBD as an adverse event. Importantly, pathophysiological studies should be undertaken to further elucidate the underlying mechanism behind any such association. Clinicians should be aware of this association and a cautious approach should be undertaken while prescribing DPP-4i in a predisposed individual or those who show clinical features suggestive of IBD.

DPP-4I USE AND RISK OF AUTOIMMUNE JOINT DISEASES

The relationship between use of DPP-4i and different joint disorders is a complex one. The joint involvement can be either arthritis or arthralgia, which is not attributable to a specific autoimmune pathology.

Nonspecific autoimmune arthritis/arthralgia

The FDA's Adverse Event Reporting System database found 33 cases of severe arthralgia reported with the use of DPP-4i. The reported DPP-4is were sitagliptin followed by saxagliptin, linagliptin, vildagliptin, and alogliptin suggesting a class effect of these drugs. In five cases, arthralgia was also reported even after switching to another DPP-4i. Following this data, the FDA published a safety warning declaring that DPP-4i may cause severe joint pain, with a time to event ranging from 1 d to years in August 2015[3]. Mascolo *et al*[102] summarised 22 published cases of DPP-4i induced arthralgia/arthritis. The duration of DPP-4i therapy before joint symptoms ranged from 2 wk to 31 mo. All these cases developed arthralgia following initiation of DPP-4i, and resolution of clinical features was achieved in most cases after discontinuation of the drug. Similar to the FDA review, few of these described patients experienced joint symptoms following reinstitution of the DPP-4i. The joints that were involved were small joints of the hands/feet, knee, and ankle. A study by Saito *et al* [103] identified 13 cases of multiple joint involvements in DPP-4i users and also noted improvement of symptoms within 3 mo of drug discontinuation. No patient required treatment with glucocorticoids. But 4 patients required non-steroidal anti-inflammatory drugs. A lower level of stromal derived factor-1α was noted during the active phase of joint involvement with normalisation of the values following clinical resolution. The levels of other cytokines and chemokines were not different between the groups thus warranting further research into the mechanism of DPP-4i induced

joint involvement. Moreover, in the absence of further study, clinical utility of measuring stromal derived factor-1α remains inconclusive at present.

Another study demonstrated a 3.77 times increased risk of arthralgia/arthritis among DPP-4i users, and interestingly different inflammatory markers were negative in a significant number (66%, n = 27/41) of such patients[104]. On the contrary, few studies negated the finding of an association between DPP-4i use and severe joint disease[105,106]. A meta-analysis including a total of 67 RCTs (79110 patients) showed that DPP-4is were associated with a small but statistically significant increased risk of arthralgia (RR: 1.13, 95%CI: 1.04-1.22; P = 0.003)[107]. However, the risk of development of serious arthralgia was not significant (RR: 1.44, 95%CI: 0.83–2.51; P = 0.20). Also, subgroup analyses disclosed that add-on or combination therapy and diabetes duration (> 5 years) were possible predictive factors associated with the increased risk of overall arthralgia[107]. Thus, it remains to be proven that DPP-4i induced joint involvement is truly an autoimmune phenomenon, but clinicians should be alert to this association. Importantly, thorough investigation is required to rule out specific AD when drug discontinuation does not result in relief of joint symptoms.

RA

The relationship between DPP-4i and RA is complex. In recent times, multiple population-based cohort studies evaluated the onset of RA in DPP-4i users. The United States of America health claim data from 2005 to 2012 showed that DPP-4i was associated with a 34% decreased risk of RA (HR = 0.66, 95%CI: 0.44-0.99) compared with other oral antidiabetic drugs (sulfonylureas and thiazolidinediones)[39]. This was similar to the study findings by Seong *et al*[40], who also showed a 33% decreased risk of RA (HR = 0.67; 95%CI: 0.49-0.92)[40]. In contrast, a recent large United Kingdom population-based study by Douros *et al*[108] who specifically looked for the association of DPP-4i use and the new development of RA found that DPP-4i use was not associated with a risk of incident RA compared with the use of other antidiabetic drugs (HR 1.0, 95%CI: 0.8-1.3). These findings were consistent irrespective of the duration of drug use or the types of DPP-4i[108]. Kathe *et al*[109] also reported a similar finding in their study. Indeed, a recent meta-analysis revealed a hazard ratio of 0.72 (95%CI: 0.54–0.96) for the development of RA in DPP-4i users[110]. However, this analysis had a limitation in the form of very high heterogeneity (I^2 = 75%).

On the other hand, there are few case reports of flaring of RA in remitted patients with DPP-4i use. Sasaki *et al*[111] had reported relapse of RA in a patient using sitagliptin in 2010[111]. Yokota and Igaki[112] also reported the onset of RA with sitagliptin use in an HLA predisposed (HLA-DRB1 allele) individual[112]. In a recent report, Padron *et al*[113] reported sitagliptin induced sero-negative RA in a 56-year-old patient with a long duration of diabetes. Hence, caution should be exercised while prescribing DPP-4i to a person with a history of prior RA or at risk of RA.

CONCLUSION

In summary, the relationship between DPP-4i use and the development of AD is complex and evolving. While recent studies have suggested that DPP-4i use may be associated with decreases in the incidence of composite AD, they can also result in the development of certain AD. BP is one AD that can be induced by DPP-4i, particularly in the elderly population. The increment in IBD risk is modest, but evidence is mixed and requires further studies to confirm this finding. DPP-4i can increase the risk of nonspecific arthritis and arthralgia along with flaring up of RA. However, data regarding this finding needs further validation. The association with other AD is mostly uncertain due to lack of evidence, but an astute clinician should be alert to any such events in a patient receiving DPP-4i. Future studies, particularly long-term follow-up studies, should clarify the relationship between AD and DPP-4i use. More basic research is also needed to find the exact underlying pathogenesis behind this association.

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