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SYSTEMATIC REVIEW

Potential Risks Related to Modulating Interleukin-13 and Interleukin-4 Signalling: A Systematic Review

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Abstract

Introduction Interleukin-13 and interleukin-4 are type-II cytokines signalling through the shared type II interleukin-4 receptor. As a result of their structural similarity, interleukin-13 and interleukin-4 have overlapping functions in the mediation of type-II-driven diseases and are, therefore, promising targets of biologic drugs currently in development for the treatment of such diseases, including asthma and atopic dermatitis.

Objective This systematic review was conducted to assess preclinical evidence of potential safety concerns related to blockade of interleukin-13 alone or interleukin-13 and interleukin-4 in combination.

Methods We specifically examined risks related to infection, malignancy and the cardiovascular system. We systematically searched the BIOSIS, MEDLINE and EMBASE databases to identify preclinical studies published between January 2006 and October 2016 that addressed the effects of interleukin-13/interleukin-4 blockade and modulation on the risk of infection, malignancy and cardiovascular events. To provide a clinical context, we also performed a search for clinical trials targeting the interleukin-13/interleukin-4 pathways. Relevant data from preclinical and clinical trials were abstracted and presented descriptively.

Results Aside from expected evidence that inhibition of interleukin-13 and interleukin-4 impaired host responses to helminth infections, we did not identify other preclinical evidence suggesting safety risks relating to infection, malignancy or cardiovascular events. We found no evidence in clinical trials suggesting serious safety concerns, i.e. increased risk for infections, malignancy or cardiovascular events from therapeutic modulation of the interleukin-13 pathway alone or the combined interleukin-13/interleukin-4 pathways.

Conclusions Although our findings are reassuring, long-term safety assessments of biologics that target the interleukin-13/interleukin-4 pathways currently in clinical development are needed.

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Key Points

Based on a systematic review of preclinical literature, inhibition of the cytokine signalling pathways of interleukin (IL)-13 and IL-4 in animal models of disease resulted in greater susceptibility to helminth infections

We did not identify any preclinical evidence of potential safety signals related to malignancy or cardiovascular events following inhibition of the IL-13/IL-4 pathways

A search of published clinical trials conducted in patients receiving agents inhibiting the IL-13/IL-4 pathways did not raise any safety concerns regarding serious infection, malignancy or cardiovascular events

1 Introduction

Interleukin (IL)-13 and IL-4 are pleiotropic cytokines that are 20–25% identical and have similar effector functions within the type-II immune response [1]. They are released by a variety of different cell types, including epithelial cells, eosinophils, basophils and mast cells, and have a broad range of overlapping biological functions, particularly in relationship to allergic diseases [2, 3].

Interleukin-13 and IL-4 both signal through the shared type-II IL-4 receptor, which is a heterodimer consisting of IL-4 receptor α (IL-4Rα) and IL-13 receptor α 1 (IL-13Rα1) [4]. Binding of IL-13 or IL-4 to this receptor activates the Jak/STAT signalling cascade, leading to the transcription of genes required for T-cell function, immunoglobulin class switching to immunogIobulin E (IgE) and antigen presentation by B cells [5]. Dysregulated IL-13 and IL-4 signalling is believed to contribute to the pathophysiology of inflammatory and allergic diseases, such as asthma and atopic dermatitis (AD) [3, 6]. Interleukin-13 also binds to IL-13 receptor α 2 (IL-13Rα2), a membrane-bound protein in humans that is present in a soluble circulating form in mice. IL-13 receptor α 2 may act as a decoy receptor to sequester extracellular IL-13, thus reducing its signalling [7]. However, potential physiological signalling functions of IL-13Rα2 are currently being investigated in pulmonary fibrosis [8], asthma [9, 10] and cancer metastasis [11, 12].

As a result of their role in mediating immunologic steps involved in the pathophysiology of asthma and AD, monoclonal antibodies (mAbs) have been developed to therapeutically block IL-13 and IL-4 signalling [3]. Clinical trials have demonstrated that targeted anti-IL-13 and anti-IL-4 therapies are beneficial in treating asthma [13] and AD [14]. Dupilumab, an anti-IL4Rα mAb, has been approved in the USA for the treatment of AD and, along with lebrikizumab and tralokinumab, has reached late-stage clinical development in asthma.

However, therapeutic modulation of the immune system using biologics has the potential for unwanted adverse effects. For example, as preclinical work has demonstrated that IL-13, IL-4 and their receptors are involved in the expulsion of parasites [3, 15], the immune response to malignant cells [16] and cardiac repair [17], modulation of these pathways could potentially increase susceptibility to certain infections, malignancy or cardiovascular events. It will therefore be important to consider these preclinical findings, as clinical development programmes for drug registration are usually too small and short in time to identify safety concerns in these areas.

The aim of this systematic review is to examine existing preclinical data on the modulation of IL-13 alone or in combination with IL-4 to determine whether there are associated potential safety signals, particularly related to infection, malignancy and cardiovascular adverse effects. In addition, we provide a clinical context through a review of emerging human safety data from clinical trials investigating agents targeting the IL-13/IL-4 pathways.

2 Methods

2.1 Systematic Literature Review of Preclinical Studies

A search methodology following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18] was developed to identify in-vivo and in-vitro preclinical studies that investigated modulation of either IL-13 alone or with IL-4, and the effects of this modulation on infections, malignancies or cardiovascular events. Searches were conducted in EMBASE, MEDLINE and BIOSIS.

All searches were conducted on 10 October, 2016, and were limited by publication date of 1 January, 2006 to 3 October, 2016. Conference abstracts and reviews were excluded. The search stage was not limited by language. Each search was developed to ensure consistency among databases. The search consisted of combinations of the following terms:

IL-13 alone or in combination with IL-4 terms AND
Adverse effects/safety/toxicology terms AND

Infection/malignancy/cardiovascular terms AND Animal/nonhuman terms OR cell line/animal cell/in vitro terms

The full search strategies are shown in Tables S1 and S2 of the Electronic Supplementary Material (ESM).

2.1.1 Systematic Literature Search Results

A total of 3032 papers were identified; 1663 papers were on IL-13 alone, and 1369 were on IL-13 and IL-4 (Fig. 1). During the first screen, the results were assessed by title and abstract by two independent individuals, with the authors making the final decision on articles that should be progressed to the second screen. At this stage, papers were included if they involved or appeared to involve modulation (up or down) of IL-13 or IL-13 and IL-4 (either through effects on the cytokines or their receptors) and if they investigated the effects of this modulation on infections, malignancies and/or the cardiovascular system. Papers were excluded based on their abstracts and titles if they were not written in English. Other reasons for exclusion were if papers were reviews that did not contain original data, they did not directly target IL-13 or IL-13 and IL-4, they were duplicates of another paper that had previously been assessed, or they did not investigate the effects of IL-13 or IL-13 and IL-4 modulation on infection, malignancies or the cardiovascular system. Studies on tumour targeting using IL-13Rα2 or the development of fibrosis as a result of parasite infection were also excluded. A total of 39 papers were included, and 2993 were excluded, at this stage.

During the second screen, the full-text manuscripts identified during the first screen were assessed for progression to the data extraction stage. This was carried out by the same two individuals as the first screen, with the authors making the final decision on articles to be included. Articles were included if the study investigated direct modulation (up or down) of IL-13 or IL-13 and IL-4 in some aspect of the research (it did not need to be the focus) and the effect on infection, malignancies or cardiovascular events. The research presented in the article also had to be of a sufficient quality standard, as determined by the use of appropriate controls, description of mouse genetic backgrounds, cell lines and cell culture techniques, and publication in a peer-reviewed journal. Papers were excluded for the same reasons as the titles and abstracts, or if the research was not of sufficient quality. Following the second

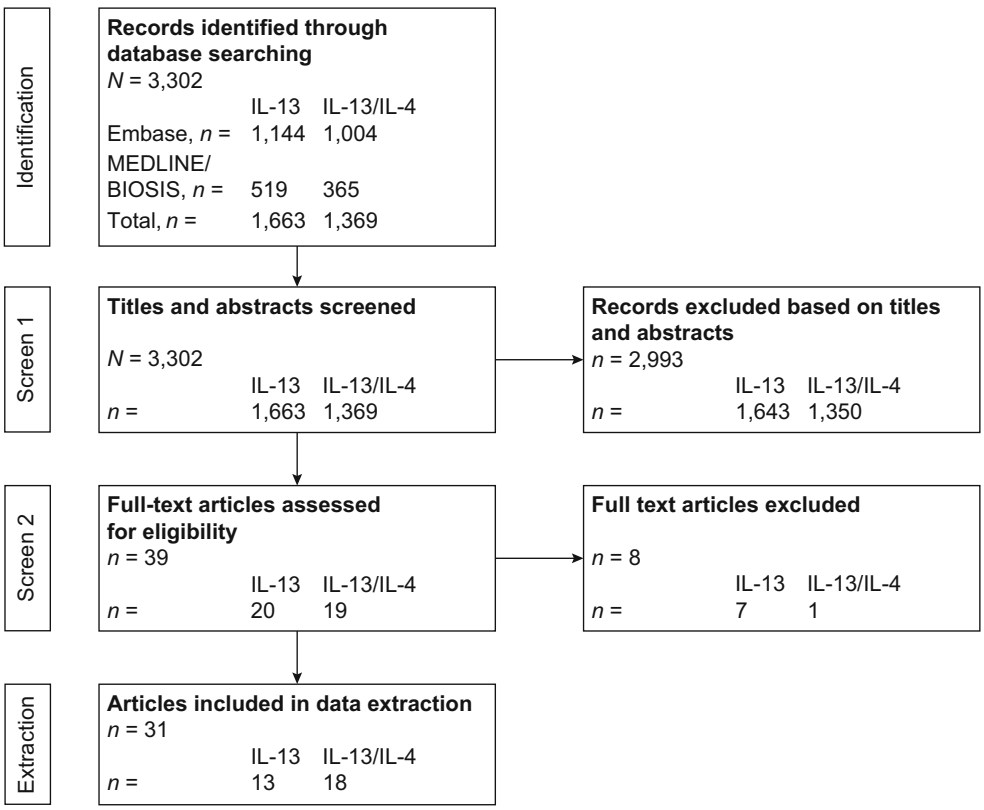

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of preclinical article selection. *IL-13/-4* interleukin-13/-4

screen, 31 papers were included, and eight were excluded for not meeting the predefined criteria.

Information was extracted from each selected full-text paper by the individuals who conducted screens 1 and 2, which was then reviewed by the authors. This information included the study design, the primary and secondary outcomes of the research, whether the study involved up- or down-modulation of IL-13 or IL-13 and IL-4, data on the effects of the IL-13 or IL-13 and IL-4 modulation on infections, malignancies or cardiovascular events, and the associated potential safety risk (none, weak or strong). Study design information included cell lines or mouse models used, tests and procedures conducted and details of any infectious organisms used. If the study did not specify the primary outcome, the outcome of most interest for the purpose of this review was identified. The authors of the papers selected for data extraction were not contacted to provide additional information.

2.2 Supplemental Literature Review of Clinical Studies

To provide a clinical context for the preclinical systematic search, a supplemental non-systematic literature search was also conducted to identify clinical trials that involved modulation of either IL-13 or IL-13 and IL-4. As this search was conducted to enrich the preclinical search, the clinical trial terms used were limited to titles only and therefore the search was not systematic. This search was carried out on 3 October, 2016 using EMBASE, and MEDLINE and BIOSIS through Proquest. The search strategy used was similar to that of the systematic search:

IL-13 alone OR IL-13 and IL-4 terms AND
Adverse effects/safety/toxicology terms AND
Infection/malignancy/cardiovascular terms AND
Clinical trial terms

The full search strategies for the supplemental search are shown in Tables S3 and S4 of the ESM.

2.2.1 Supplemental Clinical Literature Search Results

A total of 294 papers were identified; 141 of these reported data on IL-13 modulation and 153 on IL-13 and IL-4 (Fig. 2). During the first screen, the titles and abstracts of these articles were assessed to identify clinical trials that involved the modulation of IL-13 or IL-13 and IL-4. This was carried out by the same two individuals who conducted the systematic preclinical search, with the authors confirming the papers that should be progressed to the second screen. Of the 294 papers initially identified, 28 were included for further review. Articles were excluded if they were not written in English, were reviews that did not contain original data, or if the agents evaluated did not directly target IL-13 or IL-13 and IL-4. In the course of our analysis, additional papers of possible clinical interest were identified, broadly relating to the effects of IL-13 or IL-13/IL-4 modulation on the efficacy of human immunodeficiency virus vaccination, ischaemic injury and neuroprotection. Details of these papers can be found in the ESM.

For the second screen, the full-text manuscripts identified in the first screen were assessed for progression to the data extraction stage by the two independent individuals with the final decisions made by the authors. Following the second screen, 20 papers were included, and eight were excluded. In addition to the exclusion criteria used for the titles and abstracts, articles were excluded if they did not report data from a clinical trial, if the trial was not of sufficient quality or if they did not present safety data. Quality of the clinical trials was assessed based on randomisation, blinding, placebo control and publication in a peer-reviewed journal. Information on the study design, inclusion and exclusion criteria, primary and secondary endpoints and adverse event (AE) data on infections, malignancies and cardiovascular events was extracted. It was also noted whether the study involved up- or down-modulation of IL-13 or IL-13 and IL-4. The authors of the papers selected for data extraction were not contacted to provide additional information.

3 Results

Full details of the results can be found in the ESM. An overview of the findings is provided below.

3.1 Infection

The main safety signal identified was related to the effects of IL-13 and IL-4 modulation on host responses to infection with helminthic parasites. Inhibition of signalling of both IL-13 and IL-4 (either of the cytokines themselves or through IL-4Rα) was found to diminish host immune responses, such as IgE production and recruitment of immune cells to gastrointestinal helminthic parasite infections. Inhibition of signalling resulted in reduced worm expulsion and increased parasite fecundity [19, 20]. However, knockout (KO) of IL-13 alone did not inhibit expulsion of *Schistosoma mansoni* [21], and inhibition of IL-4Rα led to an eventual reduction in numbers of *Strongyloides venezuelensis* induced by IL-4 through alternative IL-4Rα-independent pathways [20].

Aside from the host response to helminthic parasites, signals relating to infections with other organisms were contradictory. Removal of IL-13 and IL-4 signalling by T cells, through removal of T-cell-specific IL-4Rα, conferred

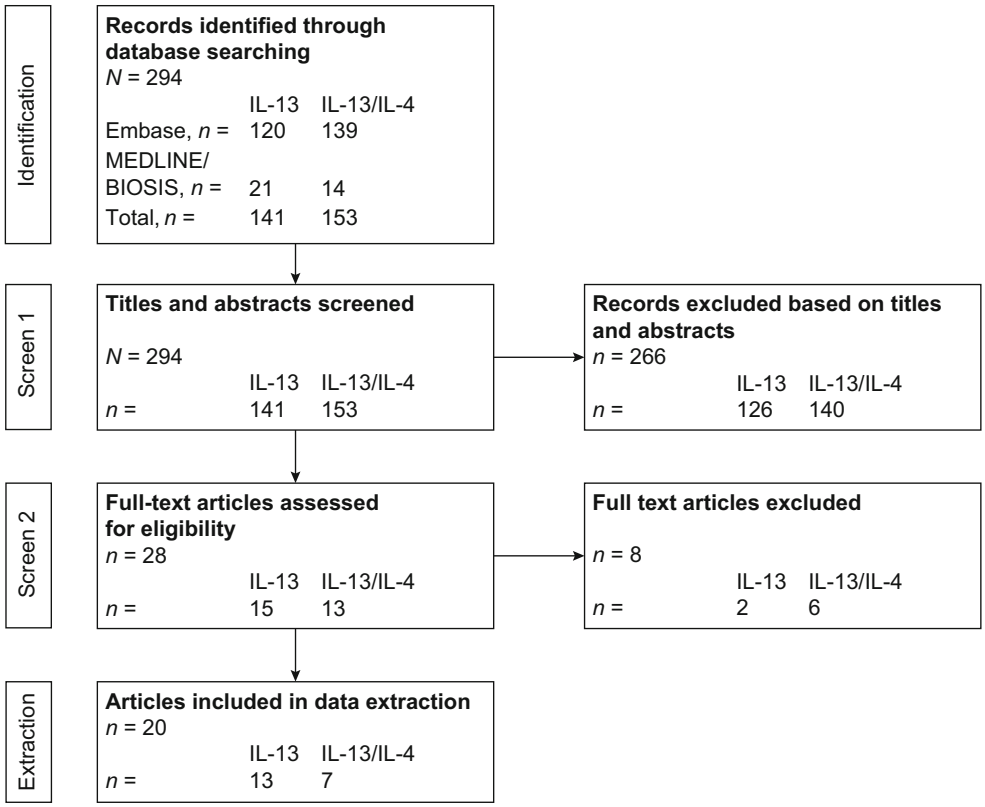

Fig. 2 Diagramshowing clinical article selection. *Non-systematic literature search. *IL-13/-4* interleukin-13/-4

resistance to *Leishmania major* infection in mice, whereas removal of global IL-4Rα led to susceptibility to disease [22, 23]. In contrast to the study in mice, IL-13 had protective properties in rats following infection with *L. major*, possibly through upregulation of IL-12 [24]. Some studies found that IL-13 and IL-4 impaired innate antiviral responses, and that KO of IL-4Rα improved these responses [25, 26]. Resistance to fungal infection with *Cryptococcus neoformans* could also be induced by inhibition of IL-13 [27]. However, there was evidence that IL-13 and IL-4 may have innate antimicrobial functions in the epithelia of the lungs [28] and the intestinal tract [29].

There were also mixed signals associated with the effects of IL-13 and IL-4 on macrophages and their ability to respond to infection. Interleukin-13 pre-treatment of macrophages that were subsequently classically activated by lipopolysaccharide was demonstrated to improve the response to *Toxoplasma gondii* infection by increasing nitric oxide production [30]. However, IL-13 and IL-4 also alternatively activate macrophages, which was found to have negative effects on their response to infection with *Mycobacterium bovis* by undermining the type-I immune response [31]. There was evidence that IL-13 and IL-4 pre-treatment also negatively affected the phagocytic ability of macrophages following infection with *Neisseria meningitidis*, possibly through inhibition of phosphoinositide 3-kinase [32].

3.2 Malignancy

In-vitro and animal studies identified a role for IL-13 and IL-4 in models of several different cancers, but this role varied depending on the tumour type. Interleukin-13 signalling exhibited anti-tumour effects in glioblastoma multiforme [33] and, following inhibition of phosphoinositide 3-kinase, androgen-independent prostate cancer [34]. Inhibition of signalling by both IL-13 and IL-4, through KO of IL-4Rα reduced the proliferation of malignant cells and increased apoptosis in a mouse model of colorectal cancer [35]. Furthermore, IL-13 and IL-4 signalling protected Hodgkin lymphoma cells from apoptosis [36] and induced programmed cell death ligand 2 expression by oesophageal carcinoma cells, potentially allowing the malignant cells to inhibit T-cell activation [37]. Interleukin-13 and IL-4 had opposing effects on skin carcinogenesis caused by the carcinogens DMBA (7,12-dimethylbenz(a)anthracene) and DMBA-TPA (12-*O*-tetradecanoylphorbol-13-acetate), with inhibition of IL-13 resulting in a greater number and size of skin tumours, whilst IL-4 inhibition led to a reduction in skin

carcinogenesis [38]. Conversely, in one model of breast cancer, inhibition of IL-13 signalling slowed tumour development, whilst IL-4 inhibition had no effect [39]. In a second breast cancer model, inhibition of signalling of both cytokines led to a reduction in tumour development and metastasis [40].

There was evidence that IL-13 and IL-4 may have roles in the development of some cancers. One study determined that expression of IL-13 by Hodgkin lymphoma cells may be responsible for the phenotypic differences between Hodgkin lymphoma and primary mediastinal B-cell lymphoma [41]. Interleukin-13 might also contribute to fibrosis in pancreatic cancer [42]. In colorectal cancer, signalling of both cytokines via IL-4Rα had stage-specific effects, with reduced IL-4Rα signalling associated with increased initiation of malignancy and risk, but also protection against tumour progression. The authors cautioned that these protective effects could be lost through the inhibition of IL-4Rα for the treatment of asthma [43].

IL-13 receptor α 2 was found to be upregulated in several tumour types. Inhibition of IL-13Rα2, and the subsequent effects on IL-13 signalling, was either beneficial or deleterious depending on tumour type [33, 44, 45]. In a breast cancer model, inhibition of IL-13Rα2 led to increased IL-13 signalling and slower tumour growth [44]. In a colorectal cancer model, IL-13Rα2 was demonstrated to be necessary for the pro-tumour downstream effects of IL-13 via upregulation of 11β-hydroxysteroid dehydrogenase type-II expression. In this model, KO of IL-13Rα2 reduced expression of 11β-hydroxysteroid dehydrogenase type-II, the further inhibition of which abrogated the pro-tumour effects of IL-13 [45]. Inhibition of IL-13Rα2 in a glioblastoma multiforme cell line (U87) allowed for normal IL-13 signalling via IL-13Rα1 that had protective effects through the induction of apoptosis [33]. This conflicted with evidence in a glioblastoma astrocytoma cell line (U251), in which IL-13 promoted cell growth, migration and invasion [46]. In terms of the role of IL-4Rα in cancer, it was found that, in mouse breast cancer cells, silencing of IL-4Rα inhibited growth at metastatic sites [40].

3.3 Cardiovascular Event

Comparatively few papers were identified that discussed the effects of IL-13 on the cardiovascular system. A mouse model demonstrated that the myocardium expresses IL-13 following a myocardial infarction, which promoted wound healing within the infarct zone. Deficiency of IL-13 could therefore negatively affect outcomes following myocardial infarction [47]. Furthermore, IL-13 was found to be protective against atherosclerosis by decreasing the numbers of pro-atherosclerotic macrophages within plaques and increasing the numbers of alternatively activated macrophages [48]. Conversely, both IL-13 and IL-4 were found to contribute to *S. mansoni*-associated pulmonary arterial hypertension, which could be prevented by therapeutic inhibition of both cytokines following treatment of the parasitic infection [49].

3.4 Context from Clinical Trials

We identified 20 publications that provided AE data from clinical trials involving interventions that targeted the signalling pathway of either IL-13 alone (tralokinumab, lebrikizumab, GSK679586 and anrukinzumab) [50–62] or IL-13 and IL-4 by blocking IL-4Rα (dupilumab, pitrakinra and AMG317) [63–69] [Table 1 and Table S5 of the ESM]. A total of 25 trials were reported in the identified publications, providing data from a total of 3883 participants studied in asthma (16 trials), ulcerative colitis (two trials), AD (five trials) and nasal polyposis (one trial). In addition, information was available for 62 healthy volunteers [two trials (one trial consisted of both patients with asthma and healthy volunteers)]. Three of the studies were single-dose pharmacokinetics studies and thus only limited safety data were available [52, 57, 60]. Of those trials that involved multiple doses, treatment durations ranged from 4 to 52 weeks (Table S5 of the ESM). Overall, the most commonly reported AE of interest to this review was nasopharyngitis, regardless of study intervention. Four instances of infection-, malignancy- or cardiovascular-related AEs that were considered related to study interventions were reported in the studies identified (Table 1). There was no evidence of reactivation of latent infections such as hepatitis B or tuberculosis, other mycobacterial infections, invasive fungal infection or unusual opportunistic infections identified in any study. There were also few treatment-related serious AEs reported, and no serious clinically significant safety concerns identified.

We identified one clinical trial of AMG317, an IL-4Rα antagonist, in patients with moderate-to-severe asthma, which reported one patient receiving AMG317 who withdrew from the study because of an upper respiratory tract infection. However, none of the AEs during this 12-week trial were considered related to the study drug [63].

Two patients experienced active treatment-related urinary tract infections in a 14-week trial of anrukinzumab, an anti-IL-13 mAb, in patients with ulcerative colitis. In the same study, one patient also receiving active treatment withdrew from the study because of treatment-related bronchopneumonia [50].

During a 16-week trial of the anti-IL-4Rα mAb dupilumab in patients with AD, there was an increased incidence of cutaneous herpes infection following dupilumab treatment compared with placebo (8 vs. 2%, respectively).

Table 1 Summary of patients experiencing adverse events (AEs) relating to infection, malignancy and cardiovascular (CV) events identified from clinical trials[a]

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
IL-13-targeting agents							
Asthma							
De Boever [51][a]	Placebo *n* = 99	Total infections of interest	0	Total malignancies	0	Total CV events	3 (3)
						Hypertension (REL)	3 (3)
Treatment duration: 8 weeks	GSK679586						
	10 mg/kg *n* = 99	Total infections of interest	1 (1)	Total malignancies	0	Total CV events	1 (1)
		Parasitic agent				Supraventricular extrasystoles (SAE; REL)	1 (1)
		Parasite-positive stool (REL; DC)	1 (1)				
Hodsman [52][b]							
Part 1	Placebo *n* = 8	Total infections of interest	0	Total malignancies	0	Total CV events	0
Treatment duration: single dose	GSK679586						
	0.005 mg/kg *n* = 3	Total infections of interest	0	Total malignancies	0	Total CV events	0
	0.05 mg/kg *n* = 3	Total infections of interest	0	Total malignancies	0	Total CV events	0
	0.5 mg/kg *n* = 6	Total infections of interest	0	Total malignancies	0	Total CV events	0
	2.5 mg/kg *n* = 6	Total infections of interest	0	Total malignancies	0	Total CV events	0
	10 mg/kg *n* = 6	Total infections of interest	0	Total malignancies	0	Total CV events	0
Part 2	Placebo *n* = 7	Total infections of interest	0	Total malignancies	0	Total CV events	0
Treatment duration: 4 weeks	GSK679586						
	2.5 mg/kg *n* = 6	Total infections of interest	0	Total malignancies	0	Total CV events	0
	10 mg/kg *n* = 6	Total infections of interest	2 (33)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza	2 (33)				
	20 mg/kg *n* = 9	Total infections of interest	0	Total malignancies	0	Total CV events	1 (11)
						Vasovagal syncope (SAE; DC)	1 (11)
Corren [53][c]	Placebo *n* = 112	All infections or infestations[d]	55 (49)	Total malignancies	1 (1)	Total CV events	5 (5)
Treatment duration: 6 months		Unknown agent		Breast cancer (DC)	1 (1)	Cardiac disorder[d]	1 (1)
		Community-acquired pneumonia (SAE)	1 (1)			Vascular disorder[d]	4 (4)
	Lebrikizumab						
	250 mg *n* = 106	All infections or infestations[d]	51 (48)	Total malignancies	0	Total CV events	3 (3)
		Viral agent				Vascular disorder[d]	2 (2)
		Shingles (SAE)	1 (1)			Cardiac disorder[d]	1 (1)
		Bacterial agent					
		Acute purulent meningitis (SAE)	1 (1)				

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
Hanania [54][e]	Placebo *n* = 116	All infections[d]	62 (53)	Total malignancies	1 (1)	Total CV events	0
Treatment duration: 28–52 weeks		Viral agent		Skin papilloma	1 (1)		
		Influenza	5 (4)				
	Lebrikizumab						
	37.5 mg *n* = 117	All infections[d]	54 (46)	Total malignancies	2 (2)	Total CV events	0
		Viral agent		Breast cancer	1 (1)		
		Influenza	3 (3)	Benign pituitary tumour	1 (1)		
	125 mg *n* = 112	All infections[d]	68 (61)	Total malignancies	1 (1)	Total CV events	0
		Viral agent		Uterine leiomyoma	1 (1)		
		Influenza	7 (6)				
		Bacterial agent					
		Gonococcal arthritis (SAE)	1 (2)				
	250 mg *n* = 118	All infections[d]	60 (51)	Total malignancies	2 (2)	Total CV events	1 (1)
		Viral agent		Intraductal proliferative breast lesion	1 (1)	Syncope (SAE)	1 (1)
		Influenza	6 (5)	Non-Hodgkin lymphoma (SAE)	1 (1)		
Noonan [55]	Placebo *n* = 52	Total infections of interest	0	Total malignancies	0	Total CV events	0
Treatment duration: 12 weeks	Lebrikizumab						
	125, 250, 500 mg/kg *n* = 157[f]	Total infections of interest	2 (1)	Total malignancies	0	Total CV events	0
		Unknown agent					
		Sinusitis (DC)	1 (1)				
		URTI (DC)	1 (1)				
Scheerens [56][g]	Placebo *n* = 16	Total infections of interest	0	Total malignancies	0	Total CV events	0
Treatment duration: 12 weeks	Lebrikizumab						
	5 mg/kg *n* = 13	Total infections of interest	0	Total malignancies	0	Total CV events	0
Baverel [57][h]	Tralokinumab						
Treatment duration: single dose	300 mg *n* = 20	Total infections of interest	0	Total malignancies	0	Total CV events	0

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
Brightling [58][i]	Placebo *n* = 151	Total infections of interest	31 (21)	Total malignancies	0	Total CV events	6 (4)
Treatment duration: 48 or 50 weeks		Viral agent				Hypertension	6 (4)
		Influenza	13 (9)				
		Unknown agent					
		Bronchitis (SEV)	4 (3)				
		Gastroenteritis (DC *n* = 1 [0.7%])	10 (7)				
		Sinusitis (SEV)	4 (3)				
		Pneumonia (SAE; REL; DC)	1 (1)				
	Tralokinumab						
	300 mg Q2W *n* = 150	Total infections of interest	20 (13)	Total malignancies	0	Total CV events	9 (6)
		Viral agent				Hypertension	8 (5)
		Influenza	11 (7)			Myocarditis (DC)	1 (1)
		Bacterial agent					
		Pneumococcal pneumonia (SAE; REL)	1 (1)				
		Unknown agent					
		Gastroenteritis	8 (5)				
	300 mg Q2W/Q4W *n* = 151	Total infections of interest	22 (15)	Total malignancies	0	Total CV events	11 (7)
		Viral agent				Cardiac failure (DTH)	1 (1)
		Influenza	14 (9)			Hypertension	9 (6)
		Bacterial agent					
		Septic shock (DTH)	1 (1)				
		Unknown agent					
		Bronchitis (SEV)	2 (1)				
		Gastroenteritis	6 (4)				
Oh [60][c]	Tralokinumab						
Treatment duration: single dose	150 mg IV *n* = 10	Total infections of interest	0	Total malignancies	0	Total CV events	0
	150 mg SC *n* = 10	Total infections of interest	0	Total malignancies	0	Total CV events	0
	300 mg SC *n* = 10	Total infections of interest	0	Total malignancies	2 (20)	Total CV events	0
				Breast mass	1 (10)		
				Melanocytic naevus	1 (10)		

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
Piper [61][k]	Placebo *n* = 47	Total infections of interest	2 (4)	Total malignancies	0	Total CV events	1 (2)
Treatment duration: 12 weeks		Viral agent				Cardiorespiratory arrest (SAE; DTH)	1 (2)
		Influenza-like illness	2 (4)				
	Tralokinumab						
	150 mg *n* = 47	Total infections of interest	4 (9)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza-like illness	1 (2)				
		Bacterial agent					
		Bacteriuria	2 (4)				
		Unknown agent					
		Sinusitis (SAE)	1 (2)				
	300 mg *n* = 51	Total infections of interest	2 (4)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza-like illness	2 (4)				
	600 mg *n* = 48	Total infections of interest	7 (15)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza-like illness	3 (6)				
		Bacterial agent					
		Bacteriuria	4 (8)				
Singh [62][c]	Placebo *n* = 4	Total infections of interest	1 (25)	Total malignancies	0	Total CV events	0
Treatment duration: 56 days		Unknown agent					
		Respiratory tract infection (DC)	1 (25)				
	Tralokinumab						
	1 mg/kg *n* = 8	Total infections of interest	2 (25)	Total malignancies	0	Total CV events	0
		Unknown agent					
		Respiratory tract infection (DC)	2 (25)				
	5 mg/kg *n* = 8	Total infections of interest	1 (13)	Total malignancies	0	Total CV events	0
		Unknown agent					
		Chest infection (SAE; DC)	1 (13)				
	10 mg/kg *n* = 3	Total infections of interest	1 (33)	Total malignancies	0	Total CV events	0
		Unknown agent					
		Respiratory tract infection (DC)	1 (33)				
IL-13 targeting agents							
Ulcerative colitis							
Reinisch [50][l]	Placebo *n* = 21	Total infections of interest	0	Total malignancies	0	Total CV events	0
Treatment duration: 14 weeks	Anrukinzumab						
	200 mg *n* = 21	Total infections of interest	0	Total malignancies	0	Total CV events	0
	400 mg *n* = 21	Total infections of interest	0	Total malignancies	0	Total CV events	0
	600 mg *n* = 21	Total infections of interest	1 (5)	Total malignancies	0	Total CV events	0
		Unknown agent					
		Bronchopneumonia (REL; DC)	1 (5)				

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
Danese [59][m]	Placebo *n* = 55	Total infections of interest	4 (7)	Total malignancies	0	Total CV events	0
Treatment duration: 12 weeks		Viral agent					
		Influenza	4 (7)				
	Tralokinumab						
	300 mg *n* = 55	Total infections of interest	2 (4)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza	2 (4)				
IL-4Rα-targeting agents							
Asthma							
Corren [63][k]	Placebo *n* = 74	Total infections of interest	2 (3)	Total malignancies	0	Total CV events	1 (1)
Treatment duration: 12 weeks		Viral agent				Irregular heartbeat (SAE)	1 (1)
		Viral gastroenteritis	2 (3)				
	AMG317						
	75 mg/kg *n* = 72	Total infections of interest	2 (3)	Total malignancies	0	Total CV events	0
		Viral agent					
		Viral gastroenteritis	2 (3)				
	150 mg/kg *n* = 73	Total infections of interest	0	Total malignancies	0	Total CV events	0
	300 mg/kg *n* = 72	Total infections of interest	4 (6)	Total malignancies	0	Total CV events	0
		Viral agent					
		Viral gastroenteritis	4 (6)				
Wenzel [67][n]	Placebo *n* = 52	Total infections of interest	5 (10)	Total malignancies	0	Total CV events	0
Treatment duration: 12 weeks		Viral agent					
		Viral gastroenteritis	3 (6)				
		Unknown agent					
		Asthma exacerbation with pneumonia (SAE)	1 (2)				
		URTI (DC)	1 (2)				
	Dupilumab						
	300 mg *n* = 52	Total infections of interest	0	Total malignancies	0	Total CV events	0

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
Wenzel [68][p]	Placebo *n* = 158	Total infections of interest	9 (6)	Total malignancies	0	Total CV events	0
Treatment duration: 24 weeks		Viral agent					
		Herpes viral infection[q]	1 (1)				
		Influenza	5 (3)				
		Bacterial agent					
		Bacterial infection[q]	3 (2)				
	Dupilumab						
	200 mg Q4W *n* = 150	Total infections of interest	11 (7)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza	10 (7)				
		Herpes viral infection[q]	1 (1)				
	300 mg Q4W *n* = 157	Total infections of interest	15 (10)	Total malignancies	1 (1)	Total CV events	2 (1)
		Viral agent		Metastatic gastric cancer (SAE; DTH)	1 (1)	Acute cardiac failure (SAE; DTH)	1 (1)
		Influenza	13 (8)			Cor pulmonale (SAE; DTH)	1 (1)
		Bacterial agent					
		Bacterial infection[q]	2 (1)				
	200 mg Q2W *n* = 148	Total infections of interest	7 (5)	Total malignancies	0	Total CV events	0
		Viral agent					
		Influenza	6 (4)				
		Bacterial agent					
		Bacterial infection[q]	1 (1)				
	300 mg Q2W *n* = 156	Total infections of interest	13 (8)	Total malignancies	0	Total CV events	0
		Viral agent					
		Herpes viral infection[q]	2 (1)				
		Influenza	9 (6)				
		Bacterial agent					
		Bacterial infection[q]	2 (1)				
Wenzel [69][r]							
Treatment duration: 28 days							
Study 1	Placebo *n* = 12	All infections[d]	3 (25)	Total malignancies	0	Total CV events	0
	Pitrakinra						
	25 mg *n* = 12	All infections[d]	1 (8)	Total malignancies	0	Total CV events	0
Study 2	Placebo *n* = 16	Total infections of interest	0	Total malignancies	0	Total CV events	0
	Pitrakinra						
	60 mg *n* = 16	Total infections of interest	0	Total malignancies	0	Total CV events	0
IL-4Rα-targeting agents							
Atopic dermatitis							
Beck [65][k]							
M4A and M4B	Placebo *n* = 16	Total infections of interest	3 (19)	Total malignancies	1 (6)	Total CV events	0
Treatment duration: 4 weeks							

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
		Bacterial agent		Mycosis fungoides (SAE)	1 (6)[i]		
		Cellulitis	1 (6)				
		Unknown agent					
		Skin infection	1 (6)				
	Dupilumab						
	75, 150, 300 mg *n* = 51[f]	Total infections of interest	2 (4)	Total malignancies	0	Total CV events	0
		Bacterial agent					
		Cellulitis	2 (4)				
M12	Placebo *n* = 54	Total infections of interest	14 (26)	Total malignancies	0	Total CV events	1 (2)
Treatment duration: 12 weeks		Viral agent				Angina pectoris (SAE)	1 (2)
		Eczema herpeticum (SAE *n* = 1)	2 (4)				
		Bacterial agent					
		Impetigo	3 (6)				
		Skin bacterial infection (SAE *n* = 1)	3 (6)				
		Anorectal cellulitis	1 (2)				
		Cellulitis (SAE)	1 (2)				
		Folliculitis	1 (2)				
		Unknown agent					
		Skin infection	2 (4)				
		Infected dermatitis	1 (2)				
	Dupilumab						
	300 mg *n* = 55	Total infections of interest	3 (6)	Total malignancies	0	Total CV events	0
		Bacterial agent					
		Impetigo	1 (2)				
		Unknown agent					
		Infected blister	1 (2)				
		Pustular rash	1 (2)				
C4	Placebo *n* = 10	Total infections of interest	1 (10)	Total malignancies	0	Total CV events	0
Treatment duration: 4 weeks		Bacterial agent					
		Skin bacterial infection	1 (10)				
	Dupilumab						
	300 mg *n* = 21	Total infections of interest	1 (5)	Total malignancies	0	Total CV events	0
		Bacterial agent					
		Skin bacterial infection	1 (5)				

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
Thaçi [66][k]	Placebo *n* = 61	Total infections of interest	21 (34)	Total malignancies	0	Total CV events	0
Treatment duration: 16 weeks		Viral agent					
		Viral infection NEC[q]	6 (10)				
		Herpes zoster	1 (2)				
		Bacterial agent					
		Bacterial infections NEC[q]	7 (2)				
		Unknown agent					
		Skin structures and soft-tissue infection[q]	5 (8)				
		Conjunctival infections, irritations and inflammation[q]	2 (3)				
	Dupilumab						
	300 mg QWK *n* = 63	Total infections of interest	26 (41)	Total malignancies	0	Total CV events	0
		Viral agent					
		Viral infection NEC[q]	5 (8)				
		Herpes simplex	1 (2)				
		Eczema herpeticum	1 (2)				
		Herpes zoster	1 (2)				
		Viral illness (SAE)	1 (2)				
		Bacterial agent					
		Bacterial infections NEC[q]	7 (11)				
		Unknown agent					
		Conjunctival infections, irritations, irritations and inflammation[q]	7 (11)				
		Skin structures and soft-tissue infection[q]	3 (5)				
	300 mg Q2W *n* = 64	Total infections of interest	21 (33)	Total malignancies	0	Total CV events	0
		Viral agent					
		Viral infection NEC[q]	4 (6)				
		Oral herpes	3 (5)				
		Herpes simplex	2 (3)				
		Bacterial agent					
		Bacterial infections NEC[q]	4 (6)				
		Unknown agent					
		Skin structures and soft-tissue infections[q]	5 (8)				
		Conjunctival infections, irritations and inflammation[q]	3 (5)				

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
	200 mg Q2W *n* = 61	Total infections of interest	36 (59)	Total malignancies	0	Total CV events	0
		Viral agent					
		Herpes simplex	3 (5)				
		Oral herpes	2 (3)				
		Viral infection NEC[q]	2 (3)				
		Bacterial agent					
		Bacterial infection NEC[q]	4 (7)				
		Unknown agent					
		Conjunctival infections, irritations and inflammation[q]	6 (10)				
		Skin structures and soft-tissue infections[q]	5 (8)				
	300 mg Q4W *n* = 65	Total infections of interest	19 (29)	Total malignancies	0	Total CV events	0
		Viral agent					
		Oral herpes	3 (5)				
		Viral infections NEC[q]	3 (5)				
		Herpes simplex	1 (2)				
		Bacterial agent					
		Bacterial infections NEC[q]	4 (6)				
		Peritonsillar abscess (SAE)	1 (2)				
		Unknown agent					
		Skin structures and soft-tissue infections[q]	3 (5)				
		Conjunctival infections, irritations and inflammation[q]	4 (6)				
	100 mg Q4W *n* = 65	Total infections of interest	27 (42)	Total malignancies	0	Total CV events	0
		Viral agent					
		Herpes simplex	5 (8)				
		Oral herpes	5 (8)				
		Viral infections NEC[q]	3 (5)				
		Herpes virus infection	1 (2)				
		Bacterial agent					
		Bacterial infections NEC[q]	6 (9)				
		Cellulitis (SAE)	1 (2)				
		Unknown agent					
		Skin structures and soft-tissue infections[q]	5 (8)				
		Conjunctival infections, irritations and inflammation[q]	1 (2)				

Table 1 continued

Reference	Drug	Infection	*n* (%)	Malignancy	*n* (%)	CV events	*n* (%)
IL-4Rα-targeting agents							
Nasal polyposis							
Bachert [64][g]	Placebo *n* = 30	Total infections of interest	2 (7)	Total malignancies	1 (3)	Total CV events	2 (7)
Treatment duration: 16 weeks		Unknown agent		Uterine cancer (SAE)	1 (3)	Transient ischaemic attack (SAE)	1 (3)
		Otitis media (DC)	1 (3)			Hypertension (DC)	1 (3)
		Bronchitis (DC)	1 (3)				
	Dupilumab						
	300 mg *n* = 30	Total infections of interest	1 (3)	Total malignancies	0	Total CV events	1 (3)
		Viral agent				Arrhythmia (SAE)	1 (3)
		Herpes zoster (SAE)	1 (3)				

DC adverse event leading to discontinuation, *DTH* resulting in death, *IL* interleukin, *IV* intravenous, *NEC* not otherwise classified, *Q2W* twice weekly, *Q4W* four times weekly, *QWK* once weekly, *REL* considered related to study drug, *SAE* serious treatment-emergent adverse event, *SEV* severe treatment-emergent adverse event, *SC* subcutaneous, *TEAE* treatment-emergent adverse event, *URTI* upper respiratory tract infection

[a]MedDRA® preferred terms are used unless otherwise specified; only infections that would be cause for clinical concern have been included

[a]AEs reported in ≥ 3% patients in any group

[b]TEAEs reported in > 1 patient in any group

[c]AEs reported in ≥ 1 patient

[d]MedDRA® system organ class term

[e]AEs reported in > 5% of patients; all infections and neoplasms reported in ≥ 1 patient

[f]Combined doses

[g]TEAEs reported in ≥ 10% of patients in any group

[h]TEAEs reported in ≥ 1 patient

[i]TEAEs reported in > 5% of patients in any group

[k]TEAEs reported in ≥ 5% of patients in any group

[l]TEAEs reported in ≥ 3 patients in any group

[m]AEs reported in ≥ 5% of patients in any group

[n]AEs reported in ≥ 3 patients in any group

[p]TEAEs reported in ≥ 5% of patients in any group; specific TEAEs with MedDRA® high-level term reported in any patient

[q]MedDRA® high-level term

[r]TEAEs reported by system organ class in > 15% of patients in any group

However, there did not appear to be a dose–response relationship [66] and this AE was not replicated in a study of dupilumab in patients with uncontrolled persistent asthma [68]. An increased incidence of herpes viral infections has not previously been observed following dupilumab treatment, and it is not a known consequence of IL-13/IL-4 modulation. However, the authors noted that this will be an AE of interest in future clinical trials with this mAb [66]. In an analysis of four earlier trials of dupilumab (either 4 or 12 weeks of treatment), also in patients with AD, patients who received dupilumab experienced fewer skin infections (ascribed to improved skin barrier function) at a rate four times lower than patients who received placebo (0.05 infections per patient vs. 0.2 infections per patient, respectively) [65].

In an 8-week trial of the anti-IL-13 mAb GSK679586 in patients with severe asthma, one patient who received GSK679586 had a parasite-positive stool sample, which was considered treatment related and resulted in their discontinuation from the study. A separate patient also receiving GSK679586 experienced a serious treatment-related AE of supraventricular extrasystoles [51].

None of the clinical trials we identified with lebrikizumab, an anti-IL-13 mAb, reported any study drug-related AEs of interest to this review (i.e. those related to infection, malignancy or cardiovascular events). One paper, describing the results of two replicate phase IIb trials (treatment ranged from 28 to 52 weeks, with 24 weeks of follow-up) in patients with uncontrolled asthma, reported a slightly greater incidence of upper respiratory tract infection in patients receiving lebrikizumab compared with placebo. However, it was not specified whether these events were related to treatment [54].

A trial of pitrakinra, an IL-13 and IL-4 antagonist, reported no AEs related to active treatment over 28 days of treatment and 5–10 days of follow-up. In this study, a greater proportion of patients of the placebo group experienced AEs related to infection compared with those receiving pitrakinra [69].

One patient receiving active treatment every 2 weeks, in a trial of anti-IL-13 mAb tralokinumab (48–50 weeks of treatment, 22 weeks of follow-up) in patients with severe uncontrolled asthma, experienced a serious AE of pneumococcal pneumonia that was considered related to treatment. A separate patient receiving tralokinumab discontinued the study because of myocarditis, but it was not specified whether this was treatment related. Additionally, two patients receiving tralokinumab in this study died (cardiac failure and septic shock), but these events were not considered to be treatment related [58].

4 Discussion

This review assessed preclinical data to examine the safety aspects of modulation of the signalling pathways of either IL-13 alone or of both IL-13 and IL-4 in relation to infection, malignancy and cardiovascular events. To provide a clinical context for this preclinical review, existing clinical trials with agents targeting these pathways were also evaluated for safety concerns.

A potential safety risk of helminthic infections in humans was identified from the preclinical studies assessed, as downregulation of both IL-13 and IL-4 negatively affected host responses to these parasitic organisms. This finding was not unexpected owing to the central roles of IL-13 and IL-4 in the type-II immune response to helminth parasites. Innate and adaptive immune cells release IL-13 and IL-4 in response to tissue injury caused by helminths and their products. The cytokines then act via IL-4Rα to carry out downstream effector functions that result in helminth expulsion and direct killing by antibodies [70]. The use of therapeutic agents that target this pathway would thus be considered contraindicated in patients with active helminth infections, as a safety precaution during clinical development. This was reflected in the exclusion criteria of the clinical trials we analysed, with several explicitly excluding patients with a history of parasitic infection [56, 65] or prior travel to countries with a high prevalence of such infections [52, 67]. Furthermore, clinical data from trials of omalizumab, an anti-IgE mAb that also targets the type-II pathway, suggest only a modest increase of geohelminth infections associated with omalizumab treatment in high-risk areas [71]. Our analysis did not identify a preclinical safety signal associated with infections caused by bacteria, fungi or intracellular parasites.

We identified complex conflicting effects following IL-13/IL-4 pathway modulation on the risk of malignancy. The majority of the preclinical studies identified negative effects of the pathways of both IL-13 alone [42, 45, 46] and in combination with IL-4 [36, 41] in malignancy that could potentially be abrogated through therapeutic pathway inhibition. However, there were also a small number of studies that demonstrated protective effects of these pathways [33, 38], which could potentially be lost following IL-13/IL-4-targeted treatment. To add to the confusion, a study by Ingram et al. identified that inhibiting the IL-13 and IL-4 pathways by blocking IL-4Rα could have either beneficial or deleterious effects depending on the stage of cancer progression [43]. Interestingly, three of the studies analysed provided evidence that IL-13 signalling via IL-13Rα2, a component of the IL-13R currently of unknown function, could be implicated in metastasis and tumour promotion [33, 44, 45]. The apparent conflicting nature of

these findings is likely owing at least partly to the diverse models and cell lines used in the analysed studies, but it is possible they also reflect the wide variety of cancer types and the complicated molecular make-up of their associated tumour microenvironments.

In this review, we did not identify preclinical evidence suggesting cardiovascular safety concerns following modulation of the IL-13/IL-4 pathways. Our clinical literature search did not identify evidence of reactivation of latent diseases such as hepatitis B or tuberculosis following downregulation of the IL-13 and IL-4 pathways. There were a small number of cases of herpes infections reported following dupilumab treatment in AD [66], but the incidence of herpes infections with the same drug in patients with asthma was similar to placebo [68]. This was investigated further in two recent meta-analyses, which examined the risk of infection in trials with dupilumab treatment in AD. These analyses each found that in dupilumab-treated groups there was a lower risk for skin infections, and a similar rate of herpes virus infections [72, 73]. A recent trial, not included in our analysis as it was published outside of the date range searched, reported that lebrikizumab treatment in patients with uncontrolled asthma resulted in a slightly greater incidence of herpes infections compared with placebo [16 (1%) patients (combined lebrikizumab dose groups) vs. two (<1%) patients, respectively] [74]. These results do not support a relationship between modulation of the IL-13/IL-4 pathways and an increased risk for herpes virus infections. Similarly, there is little evidence for an increased risk of other serious infections in clinical trials of agents that modulate these pathways. Furthermore, none of the clinical trials we identified suggested an increased risk for new malignancies or aggravation of pre-existing diseases, including cardiovascular disease, following therapeutic targeting of the IL-13/IL-4 pathways.

Although safety data of drugs targeting the IL-13 and IL-4 pathway are reassuring, one has to consider that the duration of many of these reported trials may have been too short for malignancy events to become apparent. The external generalisability of existing clinical trials may also be questioned as, by nature, they enrol individuals with significant numbers of exclusion criteria. Patients with comorbidities and those taking some concomitant medications, who may be more predisposed to potential safety risks, are generally excluded from these trials. Furthermore, the number of patients exposed to the active agents may not provide the power needed to detect smaller differences in the incidence of the diseases. Real-world long-term safety surveillance will thus be needed for the post-marketing of these drugs to identify any increased risk for infection, malignancy or cardiovascular events. Such evidence has helped to clarify potential safety risks identified with omalizumab, an anti-IgE mAb that was the first biologic therapy to be approved for the treatment of asthma. Pooled analyses of omalizumab clinical trials had previously demonstrated apparent increases with active treatment in both malignancies [75] and cardiovascular and cerebrovascular events [76] compared with placebo. However, the larger long-term post-marketing studies and further pooled analyses were unable to replicate these findings [75, 77, 78].

Our review is well timed, as there are currently two biologic drugs that target the signalling pathways of IL-13 and IL-4 in late-stage clinical development for the treatment of asthma and AD. These are tralokinumab, a human anti-IL-13 mAb that potently and specifically prevents IL-13 from interacting with IL-13Rα1 and IL-13Rα2 [79, 80], and dupilumab, a human anti-IL-4Rα mAb that indirectly modulates signalling of IL-13 and IL-4 [67].

4.1 Study Limitations

There are several limitations of this review. We only included studies that investigated the effects of IL-13/IL-4 pathway modulation in terms of infection, malignancy and cardiovascular events. Other important potential safety risks might have been missed in our analysis. Similarly, data from studies published before 2006 and after 3 October, 2016 would not have been captured. As a result of the inclusion of data from a wide variety of preclinical models, both in vitro and in vivo, it is difficult to determine whether the preclinically observed potential signals we identified can be compared with, or translated to, humans.

5 Conclusions

A rigorous review of preclinical literature has identified only one serious safety signal for active helminth parasitic infection, and no malignancy or cardiovascular safety signals associated with modulation of the IL-13/IL-4 pathways. Complementary to these findings, there were no clear increases in the risks of infection, malignancy or cardiovascular events noted from published clinical trials of anti-IL-13, anti-IL-4 or anti-IL-4Rα therapy. Furthermore, no separate safety risks were identified for biologics targeting IL-13 alone compared with both IL-13 and IL-4. Whilst our findings are reassuring, confirmatory long-term safety data from trials of biologic therapies targeting the IL-13/IL-4 pathways and real-world post-marketing surveillance are required.

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Compliance with Ethical Standards

Conflicts of interest Nicola A. Hanania has received honoraria for serving on advisory boards for AstraZeneca, and his institution has received research grant support on his behalf. Amir Sharafkhaneh has received honoraria for serving as the Chair of a Data Safety Monitoring Board for AstraZeneca. Martin Braddock, Mats Carlsson and Gene Colice are employees of AstraZeneca.

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