T Helper 2 IL-4/IL-13 Dual Blockade with Dupilumab Is Linked to Some Emergent T Helper 17–Type Diseases, Including Seronegative Arthritis and Enthesitis/Enthesopathy, but Not to Humoral Autoimmune Diseases

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Dupilumab, an IL-4/IL-13 receptor blocker, has been linked to emergent seronegative inflammatory arthritis and psoriasis that form part of the spondyloarthropathy spectrum. We systematically investigated patterns of immune disorders, including predominantly T helper 17–(spondyloarthropathy pattern) and T helper 2–mediated disorders and humoral autoimmune pattern diseases, using VigiBase, the World Health Organization's global pharmacovigilance of adverse drug reactions. Several bioinformatics databases and repositories were mined to couple dupilumab-related immunopharmacovigilance with molecular cascades relevant to reported findings. A total of 37,848 dupilumab adverse drug reaction cases were reported, with skin, eye, and musculoskeletal systems most affected. Seronegative arthritis (OR = 9.61), psoriasis (OR = 1.48), enthesitis/enthesopathy (OR = 12.65), and iridocyclitis (OR = 3.77) were highly associated. However, ankylosing spondylitis and inflammatory bowel disease were not conclusively associated. Overall, classic polygenic humoral–mediated autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus were not associated with dupilumab use. Pathway analysis identified several biological pathways potentially involved in dupilumab–associated adverse drug reactions, including the fibroblast GF receptor (in particular, FGFR2) pathway. MicroRNAs analysis revealed the potential involvement of hsa-miR-21-5p and hsa-miR-335-5p. In conclusion, IL-4/IL-13 blockers are not unexpectedly protective against humoral autoimmune diseases but dynamically skew immune responses toward some IL-23/IL-17 cytokine pathway–related diseases. IL-4/13 axis also plays a role in homeostatic tissue repair and we noted evidence for a link with ocular and arterial pathology.

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INTRODUCTION

The seronegative spondyloarthropathy (SpA) group of conditions has a propensity toward enthesitis/enthesopathy and seronegative inflammatory arthritis, most typically characterized in psoriatic arthritis (Bridgewood et al., 2018; Schett et al., 2017). Beyond psoriatic arthritis, an array of related conditions collectively termed SpA include psoriasis, psoriatic nail disease, and ankylosing spondylitis (AS). Other diseases commonly associated with SpA include inflammatory bowel disease (IBD) and anterior uveitis (Bridgewood et al.,

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Abbreviations: AD, atopic dermatitis; ADR, adverse drug reaction; AS, ankylosing spondylitis; CrI, credible interval; IBD, inflammatory bowel disease; IC, information component; miRNA, microRNA; PRR, proportional reporting ratio; SpA, spondyloarthropathy; Th, T helper

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2018). The SpA spectrum, to varying degrees, is associated with the IL-23/IL-17 cytokine axis as indicated by immunogenetics, experimental models, and therapeutic responses after IL-23/IL-17 axis blockade and so exhibits T helper (Th) 17 features (Boutet et al., 2018).

Diseases associated with IL-4/IL-13 cytokine axis or the so-called Th2 diseases include atopic dermatitis (AD), food allergy, allergic asthma, conjunctivitis, rhinosinusitis, and a tendency toward allergic inflammation secondary to barrier function disruption (Nakayama et al., 2017). Prominent dysregulation of key cytokines, including IL-4 and IL-13, and others is strongly linked to this type of inflammation (Gandhi et al., 2017). AD features adaptive immune involvement by conventional T-cells and antibody production and class switching to both IgG and IgE (Gandhi et al., 2017). This immunopathology in the Th2 diseases is distinctive from that of the other classically described Th1 immunity where Th cells are associated with IFN-γ and TNF production, with Th1 immunity linked to granulomatosis inflammation in sarcoidosis and other conditions, but where autoantibody associations are lacking (Bäumer et al., 1997; Csernok et al., 1999).

These overarching principles have resulted in the so-called Th paradigm of Th cells regulating different types of immunopathology, including Th1-, Th2-, and Th17-type autoimmunity (Bridgewood et al., 2021a). Although the Th paradigms initially involved the idea of very distinctive T-cell lineages, it is currently known that there is quite a degree of overlap in terms of plasticity and interchangeability between the different lineages with consequent shifts in cytokine production (Murphy and Stockinger, 2010). In addition, innate lymphocytes faithfully recapitulate the Th paradigm, and non–T cells can produce some of the cytokines relevant to the concept (Artis and Spits, 2015; Bank, 2020). However, looking at the relationship between Th1, Th2, and Th17 diseases is difficult to be studied directly in vivo in humans.

Dupilumab, a fully human IL-4Rα blocker, was the first biologic approved for moderate-to-severe AD, asthma, and nasal polyposis (Bachert et al., 2016; Castro et al., 2018; Seegräber et al., 2018). By antagonizing both IL-4 and IL-13, dupilumab prevents Th2 polarization and turns off Th2 inflammation, promoting cutaneous barrier restoration, decreasing the infiltration of airway epithelium, and improving the overall cutaneous and respiratory epithelial functionalities. Since gaining approval, dupilumab has been occasionally linked to Th17-type inflammation (i.e., psoriasis) (Jaulent et al., 2021; Roesner et al., 2021). Furthermore, other IL-17–mediated musculoskeletal disorders, such as severe enthesitis/enthesopathy and seronegative arthritis (Bridgewood et al., 2021b; De Stefano et al., 2022; Willsmore et al., 2019), were also reported as case reports and case series.

Indeed, it has been pointed out that dupilumab may offer a unique opportunity to unravel the IL-4/IL-13 pathway in vivo in humans (Roesner et al., 2021). We decided to test the epidemiological link between dupilumab use and inflammatory and autoimmune disorders across the various Th paradigms by mining a global pharmacovigilance database containing dupilumab-related adverse drug reactions (ADRs). We carried out a disproportionality analysis to look at different patterns of emergent Th paradigm immunity under anti–IL-4/IL-13 therapy in a large global pharmacovigilance database. Our findings suggest a dynamically tunable Th paradigm cytokine network in vivo in humans that might have implications for immunopathology and cytokine tissue homeostasis given the key role of IL-4/IL-13 in repair beyond their seminal roles in immune responses.

RESULTS

Musculoskeletal disorders are frequently reported among dupilumab-related ADRs

Up to 9 March 2021, 94,065 ADRs from 37,848 unique reports were included and analyzed in this paper. A summary of all the ADRs stratified according to the affected organ/system is presented in Supplementary Table S1, with a focus on musculoskeletal and connective tissue–related ADRs in Supplementary Table S2. The temporal trend of dupilumab-related ADRs was analyzed, and no Weber effect (Hoffman et al., 2014), which is a peak in ADRs reported at the end of the second year after regulatory approval of the drug followed by a constant decline in reporting, could be detected. After skin and subcutaneous tissue (23,554 reports, 62.23% of the entire sample) and eye (12,147 reports, 32.09%), musculoskeletal and connective tissue are the third most affected system (with 3,452 reported ADRs, 9.12%).

Dupilumab and Th17-type disease

The top musculoskeletal ADRs were arthralgia (1,225 reports, information component $[IC]_{0.25} = 1.04$, OR = 2.22, 95% credible interval [CrI] = 2.09–2.35) and joint swelling (190 reports, $IC_{0.25} = 0.67$, OR = 1.85, 95% CrI = 1.61–2.14), with arthralgia and joint swelling being commoner (Supplementary Table S2). However, back pain was underrepresented (175 reports, $IC_{0.25} = -1.09$, OR = 0.54, 95% CrI = 0.47–0.63),

Overall, some diseases with Th17 immunogenetics and immunology were associated with dupilumab use (Figure 1). Among these diseases, seronegative arthritis ($IC_{0.25} = 0.05$, OR = 9.61, 95% CrI = 3.07–30.07), psoriasis ($IC_{0.25} = 0.36$, OR = 1.48, 95% CrI = 1.29–1.70), enthesitis/enthesopathy ($IC_{0.25} = 1.86$, OR = 12.65, 95% CrI = 6.54–24.47), and iridocyclitis ($IC_{0.25} = 0.52$, OR = 3.77, 95% CrI = 1.88–7.55) had positive $IC_{0.25}$ values.

Interestingly, IBD and AS that are part of the IL-23/IL-17 axis SpA immunopathology spectrum were not associated with dupilumab therapy. For AS, an OR of 0.28 (95% CrI = 0.07–1.11) was computed. For IBD, a protective effect could be found. For Crohn's disease, an $IC_{0.25}$ of −2.74 and an OR of 0.26 (95% CrI = 0.16–0.45) were computed. Similarly, ulcerative colitis displayed an $IC_{0.25}$ of −1.67 and an OR of 0.54 (95% CrI = 0.33–0.88), and it is noteworthy that ulcerative colitis did not respond to the modulation of the IL-4/IL-13 pathway in clinical trials (Tilg and Kaser, 2015).

Dupilumab is not linked to classic polygenic humoral–mediated autoimmune diseases

Overall, classic polygenic humoral–mediated autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and others, were not associated with dupilumab use (OR = 0.60, 95% CrI = 0.38–0.96) (Supplementary Table S3). Interestingly, a protective effect (the so-called inverse signal) could also be showed for

coeliac disease, a classic autoimmune disease (OR = 0.22, 95% CrI = 0.05–0.87; IC = −1.95, 95% CrI = −4.54 to −0.59).

Dupilumab and diseases with Th1 features and other observations

Polygenic autoimmune–autoinflammatory disease overlap without humoral autoimmunity with Th1 features, such as giant cell arteritis, sarcoidosis, and polymyalgia rheumatic, were not found to be associated with dupilumab use (Supplementary Table S3). However, there was a positive association with acne and erythema nodosum, which exhibited positive $IC_{0.25}$ values (0.11 and 1.11, with ORs of 1.28 [95% CrI = 1.08–1.51] and 3.33 [95% CrI = 2.32–4.76], respectively).

Dupilumab may be linked to eosinophilic–associated inflammation

Among allergic and eosinophilic disorders, asthma flares and hypereosinophilic syndrome were found to be associated, with positive $IC_{0.25}$ values of 2.32 and 0.88 (ORs of 5.58 [95% CrI = 5.11–6.09] and 17.57 [95% CrI = 6.51–47.46], respectively) (Supplementary Table S3), findings in keeping with the reported eosinophilia in asthma trials (Castro et al., 2018).

Dupilumab may be linked to eye degeneration and may increase the need for cardiovascular surgery

Although IL-4/IL-13 cytokines have been mostly understood in terms of Th2 immunology, an important component of this axis pertains to tissue homeostasis and repair, and in the course of our analysis, we looked beyond inflammatory ocular and cardiovascular complications. We found that dupilumab use is associated with disorders that have been classically considered degenerative, including keratoconus (OR = 81.45, 95% CrI = 46.67–142.15) (Supplementary Table S3). Conjunctival irritation is a particularly commonly recognized complication of dupilumab (Maudinet et al., 2019) therapy and, by discomfort with consequent eye rubbing trauma, may contribute to ocular surface trauma and loss of tissue integrity with keratoconus.

Analogous to an absence of AS diagnosis linked to dupilumab therapy, we likewise found no evidence for valvular regurgitation or valvular replacement, which are known AS complications (Supplementary Table S3). However, aortic aneurysm risk was substantially increased, with an OR for aneurysms of 6.63 (95% CrI = 1.65–26.58) specifically among subjects aged ≥75 years. The overall need for cardiovascular surgery was found significantly elevated (OR = 9.10, 95% CrI = 1.26–65.55), even though $IC_{0.25}$ was negative (−2.50). In terms of bone/joint homeostasis and repair, we could not find evidence for osteoarthritis (OR = 0.45, 95% CrI = 0.29–0.71), nodal osteoarthritis (OR = 3.43, 95% CrI = 0.48–24.50), or joint arthroplasty (OR = 0.64, 95% CrI = 0.09–4.56). All dupilumab-related ADRs are pictorially summarized in Figure 1.

Bioinformatics analysis

According to the bioinformatics analysis of the mechanism of action, the following pathways were found to be potentially involved in the action of dupilumab: the focal adhesion phosphoinositide 3-kinase/protein kinase B–mTOR signaling pathway, the IL-4 and IL-13 signaling pathways, the Jak–signal transducer and activator of transcription pathway, and P73 transcription factor network.

Pathway analysis enabled us to identify the following biological pathways potentially involved in dupilumab–associated ADRs because they couple the IL-4/IL-13 axis with tissue homeostasis and repair: the fibroblast GF receptor (in particular, FGFR2), phosphoinositide 3-kinase/protein kinase B, insulin receptor, IGF1R, HER2/neu (ERBB2), MAPK, and receptor tyrosine kinase signaling pathways. In addition, the estrogen signaling cascade as well as other GFs and secondary messengers were putatively involved. Laminin interactions were also found to be associated. For other details, the reader is referred to Supplementary Table S4. After microRNA (miRNA) analysis, we found hsa-miR-21-5p and hsa-miR-335-5p as putatively linked with dupilumab-related ADRs. Their functions and roles are reported in Supplementary Table S5.

DISCUSSION

In this work, we identified over 37,000 unique case reports of dupilumab side effects reported on the World Health Organization pharmacovigilance database. We specifically categorized the patterns of disease into Th17 and Th1/Th2 like on the basis of emerging case reports of seronegative arthritis and psoriasis in subjects undergoing dupilumab therapy for AD or asthma. It could be theorized that the blocking of IL-4/IL-13 and T-cell polarization to Th2 could lead to opportunistic polarization of T cells to either Th1 or Th2 (Bridgewood et al., 2021a). Our findings from large numbers of cases provided in vivo human immunology data that support the idea that the IL-4/IL-13 axis may act as a restraint toward Th17-type disease activation in some organs, with an increased incidence of psoriatic-like disease, skin disease, nail disease, and joint disease. Both IL-4 and IL-13 are able to downregulate IL-23 from antigen-presenting cells or IL-17 from T cells and thus put a break on IL-17–driven inflammation (Bridgewood et al., 2021b). This has been shown in vitro and in numerous murine models of IL-17–driven inflammation (Guenova et al., 2015; Lubberts et al., 2000; Newcomb et al., 2012, 2009). Further work is needed to closely scrutinize the effect of shifting the Th cell balance in vivo. On the contrary, the lack of associated humoral autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus under ADR cases with dupilumab therapy may represent the well-known effect of IL-4 on antibody production, and thus blocking IL-4/IL-13 would not be expected to enhance such immunopathology (Severinson, 2014).

The role of IL-4/IL-13 in restraining psoriatic inflammation has also been evaluated clinically and two decades ago, with patients with psoriasis treated with recombinant IL-4 (n = 20) showing significant improvement in PASI scores (Ghoreschi et al., 2003), so it is not surprising that the opposite strategy may be occasionally detrimental for psoriatic disease spectrum inflammation. Furthermore, in a recent case series of dupilumab-induced psoriasis-like inflammation, the skin lesions showed increased IL-23 expression (Napolitano et al., 2021), whereas another study has successfully treated dupilumab-induced psoriasis with ustekinumab (anti–IL-12/

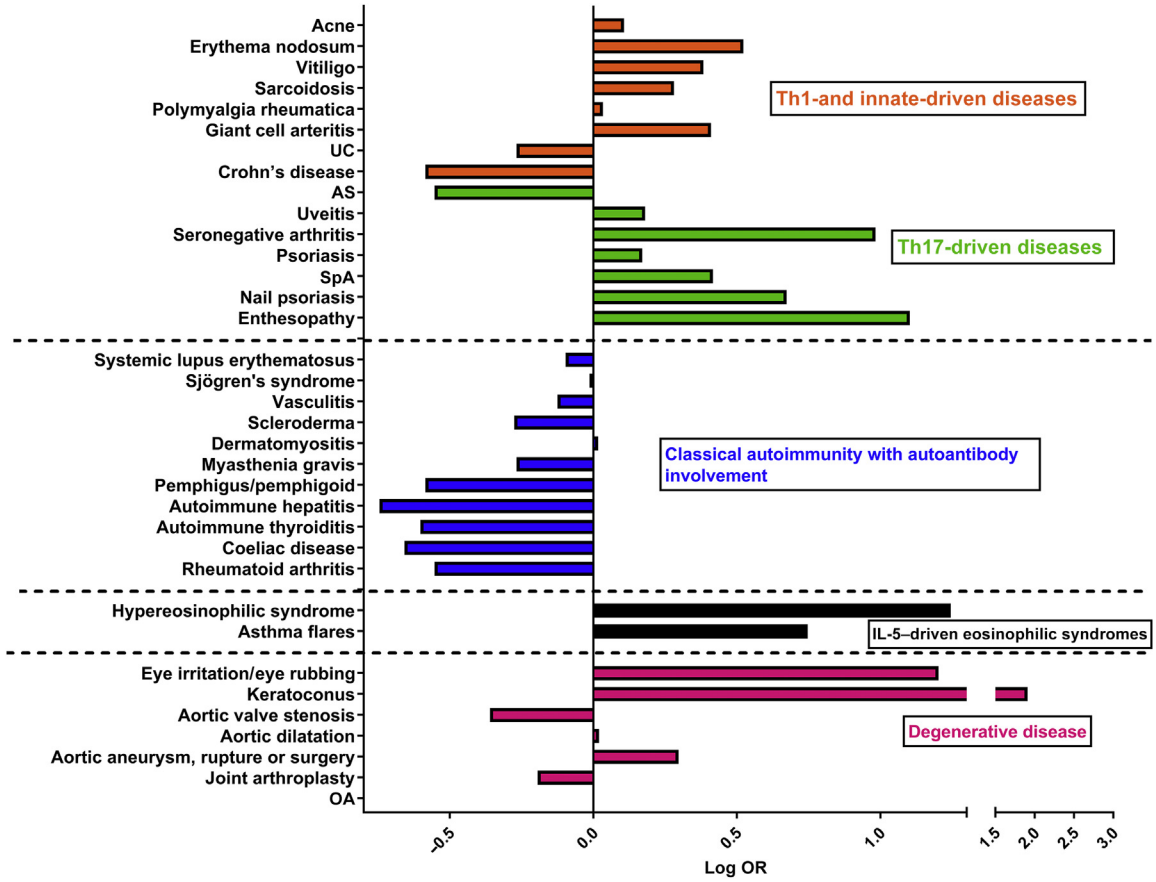

Figure 1. Patterns of diseases associated with dupilumab. Heterogeneous diseases with innate immune components and diseases with granulomatosis-associated inflammation (that is often linked to IFN-γ and TNF) are marginally affected by anti–IL-4/IL-13 therapy. Vitiligo has heterogeneous disease mechanisms, including IFN-γ pathway effector mechanisms. Of interest, Crohn's disease and UC were historically thought to be more Th1 linked but have strong Th17 pathway–related SNPs, including that in the IL-23R. However, these diseases showed no association when compared to the other family members of the human seronegative SpA-related conditions where as seronegative arthritis and enthesopathy/enthesitis were significantly more common. It is interesting that IL-13 SNPs have been linked to PsA but not to psoriasis or other family member diseases in SpA. The classical humoral–mediated autoimmune diseases were under-reported (some representative examples are shown in blue). It is noteworthy that IL-4 has multifaceted roles in B-cell biology, including maturation, Th2 differentiation, and IgG1 class switching, and this might underscore the apparently protective effect for these diseases. It has been shown that IL-4 and IL-13 blockade may be associated with the experimental emergence of dominant IL-5 cytokine pathways. This may underscore the emergence of IL-5 associated autoimmunity, including excessive eosinophilic activation leading to hypereosinophilic syndrome and eosinophilic–associated asthma, although our data could not confirm that the asthma flares were eosinophilic driven. Finally, the IL-4/IL-13 axis is associated with tissue homeostasis and repair in several sites, including the cornea and the musculoskeletal system. We complement these findings by showing a large increase in keratoconus, (which is linked to eye irritation and rubbing) and is also a potential signal for aortic vascular disease but not to aortic valve disease, (which is a feature of AS). Noting that IL-13 plays a role in cartilage biology, there was no increase in OA. AS, ankylosing spondylitis; OA, osteoarthritis; PsA, psoriatic arthritis; SpA, spondyloarthropathy; Th, T helper; UC, ulcerative colitis.

IL-23 therapy) (Jaulent et al., 2021). Of note, phenotype switching from psoriasis to AD has been reported after IL-12/IL-23 blockage (Al-Janabi et al., 2020). It is well-established in vitro that IL-4 and IL-13 downregulate IL-12 and IL-23, thus potentially serving as a brake (Bridgewood et al., 2021b; D'Andrea et al., 1995).

Our findings showed that dupilumab was linked to some SpA features but not to others, including AS and IBD. At the population level, GWASs have shown polymorphisms linked to IL-13 in psoriatic arthritis, but the functional basis for this is poorly understood (Bowes et al., 2011; Eder et al., 2011). In more detail, we took advantage of the recent observations that anti–IL-4/IL-13 therapy has been associated with the case series of patients who develop severe enthesitis, psoriasis, and uveitis (Ayasse et al., 2021; Jaulent et al., 2021; Willsmore et al., 2019). This is most unusual because the SpA and AD phenotypes are not considered to be overlapping, but we previously showed that the human enthesis contains IL-23–producing cells, the production of which is attenuated by IL-4 and IL-13 treatment (Bridgewood et al., 2021b). It is well-known that patients with AD display high levels of IL-4, a cytokine capable of negatively affecting Th17 lymphocyte function and upstream myeloid cell–driven IL-23 production (Bridgewood et al., 2021b). Thus, IL-4/IL-13 blockers may increase IL-23 and IL-17 production and consequently also trigger enthesis and seronegative arthropathy.

We also reported increased eosinophilic disorders after dupilumab treatment. Eosinophilic disorders are driven by IL-5, which can be produced and act independently of IL-4/IL-13 (Niranjan et al., 2013). Dupilumab-induced eosinophilic

disorder case reports have also been reported (Iwamuro et al., 2020; Menzella et al., 2019), and the present findings point toward an IL-5 cytokine skewing in some cases.

Moreover, in seronegative SpA and AS in particular, aortic root inflammation manifesting as valvular regurgitation is common (Palazzi et al., 2008). Similar to the role in the skin, IL-4 is also thought to play a role in vascular homeostasis (Schönbeck et al., 2002), and similar to the skin, the aortic root is a site of repeated physical biomechanical stressing and microdamage and repair owing to valvular action (Beller et al., 2004). Because the aorta is a target of seronegative SpA, we looked for reports of aortic value and related disease and found evidence for aneurysms in older subjects (aged ≥75 years). In a similar manner, eye irritation and physical irritation with eye rubbing (Supplementary Table S3) (OR = 15.92, 95% CrI = 14.94–16.96) are associated with a dramatically elevated risk of keratoconus after dupilumab therapy, and this points toward key tissue-protective roles of the IL-4/IL-13 pathway beyond the classically described roles in Th2 immunity, including antibody production such as IgE.

Furthermore, dupilumab was associated with a protective OR in IBDs (Crohn's disease and ulcerative colitis). Recently, Armandi et al. (2019) have hypothesized the use of dupilumab in IBDs targeting the IL-4 pathway. In addition, of note, numerous animal models of IBD are dependent on IL-4 and IL-13 (Fichtner–Feigl et al., 2008; Heller et al., 2002; Specht et al., 2006; Stevceva et al., 2001), and IL-4 SNPs have been linked to IBD (Klein et al., 2001; Olavesen et al., 2000). This is interesting in the light of the failure of anti–IL-13 blockers, namely tralokinumab and anrukinzumab, in some recent clinical trials in patients with ulcerative colitis (Tilg and Kaser, 2015).

Interestingly, miRNAs analysis revealed the potential involvement of hsa-miR-21-5p and hsa-miR-335-5p. hsa-miR-21-5p has been linked to the regulation of the inflammatory and immune responses, such as IL-12 and IFN-1 production and regulation and Th17 immune response. hsa-miR-21-5p has been recently identified as a major driver of psoriasis and psoriatic arthritis (Abdallah et al., 2021; Alatas et al., 2020), vitiligo (Huo et al., 2021), and autoimmune anterior uveitis/uveoretinitis (Hsu et al., 2015; Shi et al., 2019). hsa-miR-335-5p has been identified as a molecule playing a key role in the etiopathogenesis of osteoarthritis (Lu et al., 2021; Tornero-Esteban et al., 2015) and cardiovascular disease (Legaki et al., 2020).

The key strengths of this investigation include the facts that we examined a large number of individual case safety reports (>37,000) and that we used three disproportionality measures (reporting OR, proportional reporting ratio [PRR], and IC) that enabled us to more thoroughly assess drug–ADR pairwise associations. Despite this comprehensive approach, the present analysis did not account for some data shortcomings that should be properly acknowledged. Such limitations include the lack of detailed immunospecific-related data, data set heterogeneity, as well as limited number of observations for some drug–ADR pairs. Moreover, a direct causal relationship for such drug–ADR pairs cannot be inferred from these data alone and warrants further ad hoc epidemiological surveys and careful clinical assessment for proper identification and interpretation of the pharmacovigilance alert signals and further immunological and translational studies.

In conclusion, the antagonism of Th2 cytokines of IL-4 and IL-13 was associated with skewing the immune response toward Th17 and in some IL-5–related immunopathology but not toward classical humoral–mediated autoimmunity. A major role for IL-4 and IL-13 in tissue homeostasis and repair has been noted, and this report of aortic aneurysms and keratoconus raises the possibility that the skewing of such repair pathways may be linked to other seemingly degenerative-related pathologies. Thus, translational immunology studies into the effect of skewing the Th2 pathway toward other cytokines and the risk of de novo immunologically driven comorbidities are needed as is the need to decipher whether IL-4 or IL-13 plays a greater role. This is key for refining immunotherapy across the Th2 disease spectrum and beyond.

MATERIALS AND METHODS

Database

We mined data contained in VigiBase up to 9 March 2021. VigiBase is the global pharmacovigilance database developed and maintained by the World Health Organization Collaborating Centre for International Drug Monitoring, named the Uppsala Monitoring Centre (Uppsala, Sweden) (Lindquist, 2008). VigiBase contains >20 million individual case safety reports of suspected ADRs, spontaneously forwarded by >140 countries that are members of the World Health Organization's Programme for International Drug Monitoring.

Thanks to the hierarchical structure of the database, data aggregation on several levels of precision, including medicinal product level (related to the named product marketed and sold in a given country, with a specific ingredient and form/strength), is possible, and efforts were made to ensure the highest data quality as well as to minimize potential batch effects (i.e., different selection criteria for each country) (Lindquist, 2008).

Disproportionality analysis

To assess the relationship between the drug and the suspected ADR, various disproportionality measures between the observed and the expected reporting of a drug–ADR pair can be computed, including reporting OR, PRR, and IC. The latter reflects the strength of the ADR association and was originally formulated through the Bayesian Confidence Propagation Neural Network (Bate, 2007): if the lower bound of IC is a positive (or negative) value, this means that the pair under study is reported more often (or less frequently) than expected on the basis of all the reports included in VigiBase,

$$IC = \left(\frac{N_{observed} + 0.5}{N_{expected} + 0.5}\right)$$

where

$$N_{expected} = \frac{N_{drug} \cdot N_{reaction}}{N_{total}}$$

$N_{expected}$ can be defined as the number of case reports expected for the given drug effect pairwise association, whereas $N_{observed}$ can be defined as the actual number of case reports for the drug–ADR combination under study. N_{drug} is the number of all case reports for

the drug under scrutiny, regardless of the effects reported, and conversely, $N_{reaction}$ is the number of case reports for the given side effect under study, regardless of the specific type of medicine. N_{total} is the total number of reports in the database.

We also computed PRR as the proportion of ADRs for a given drug, divided by the corresponding proportion for all other drugs contained in VigiBase. From a conceptual perspective, PRR is similar to the proportional mortality ratio.

All these disproportionality measures are calculated with their 95% CrI, with $IC_{0.25}$ and $IC_{97.5}$ being the lower- and upper-bound values, respectively. In this investigation, we reported both OR, PRR, and IC because whereas $IC_{0.25}$ is the traditional threshold employed in the statistical signal detection analysis of pharmacovigilance databases, OR is more commonly utilized in the biomedical field. PRR is analogous to OR, even though only reporting OR can be used to infer relative risk, differently from PRR. However, IC is more statistically robust, being based on data mining techniques, enabling as such to curb the risk of detecting spurious statistically significant associations. IC can, indeed, provide a conservative measure of association, which is of paramount importance in the case of ADRs with very low expected frequencies extracted from a large, big data-based database such as VigiBase.

ADRs categorization and classification

The Medical Dictionary for Drug Regulatory Activities (Brown et al., 1999) ontology at the system organ class level was used to categorize suspected ADRs related to dupilumab. The patterns of immune diseases were manually curated and described according to those known to be part of the seronegative SpA group. The patterns of inflammatory diseases were categorized along the immunological disease continuum of inflammation against self, with autoimmune and innate immune–mediated pathologies at each end of the spectrum and intermediate pattern diseases in the middle (McGonagle and McDermott, 2006). We included nonhumoral-mediated autoimmune diseases that exhibit major histocompatibility complex class II associations and severe inflammation that have Th1 features, including granulomatosis disorders such as sarcoidosis and giant cell arteritis or vasculitis.

Bioinformatics analysis

Drug safety science was coupled with bioinformatics, coherently integrating patient-centered approaches assessing the drug safety profile with molecular knowledge from mechanistic modeling, computational systems pharmacology, and pharmacometrics, as detailed in Soldatos et al. (2022).

More specifically, several omics bioinformatics databases were cross-referenced and mined to provide plausible mechanisms for reported findings, including the Drug Gene Pathway meta-database meta-repository (Shah et al., 2014), which utilizes expert-curated sources and compiles data from PharmGKB, DrugBank, and the United States Food and Drug Administration's National Drug Code databases, among others. ADR-gene networks were created by mining DisGeNET (Piñero et al., 2015), which is one of the most comprehensive human gene–disease associations databases and integrates several sources, either curated and inferred ones, collecting evidence from animal models as well. STRING (Szklarczyk et al., 2021) was then utilized to convert these networks into functional ADR–protein association networks, which were finally analyzed in terms of biological pathways using Reactome (Joshi-Tope et al., 2005), a comprehensive pathway browser. Only pathways significant at the false-discovery rate analysis were considered.

The latest release of the miRNA Pathway Dictionary Database (miRPathDB 2.0) (Kehl et al., 2020) was mined to retrieve miRNAs putatively associated with dupilumab-associated ADRs. This database coherently integrates in a harmonized way several miRNAs resources, including miRbase, miRCarta, miRTarBase, TargetScan, and MiRanda (Agarwal et al., 2015; Chou et al., 2018)

Analysis of miRNA candidates was conducted through maximum coverage, a technique that enables the investigation of the maximum number of genes potentially regulated by a specific number of miRNAs. The use of manually, expertly curated, or automated artificial intelligence–enhanced bioinformatics repositories characterized by highly homogeneous, standardized annotations by means of controlled vocabularies and community-driven ontologies enabled the seamless integration and interoperability of several omics datasets and databases.

Data availability statement

Datasets related to this article can be found at https://who-umc.org/vigibase/, hosted at Vigibase (Lindquist, 2008)

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CONFLICT OF INTEREST

MW has received honoraria for educational lectures and consultancies from UCB, Novartis, Leo Pharma, AbbVie, Janssen, Sanofi, Biogen, and AstraZeneca. DM has received honoraria from Novartis, Janssen, Lilly, Pfizer, Celgene, and UCB. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CB, MW, DN, NLB, DM; Data Curation: NLB; Writing - Review and Editing: CB, MW, TM, AW, DN, KB, HA, GD, SG, NLB, DM

Disclaimer

The views expressed are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.03.013.

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