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ABSTRACT

Unprecedented successes regarding cancer immunotherapy have been achieved, in which therapeutic agents are used to target immune cells rather than cancer cells. The most effective immunotherapy to date is the group of immune checkpoint inhibitors (CPI), targeting, for example, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death protein (PD-1). TThe combination of these therapies (anti-PD-1 with anti-CTLA-4) induces high response rates, and seem to be increased further when applied in early-stage disease. However, combined CTLA-4 plus PD-1 blockade causes frequent high-grade immune-related adverse events (irAE). To date, research on biological mechanism of irAEs is scarce and no widely accepted biomarkers predicting onset of severe irAEs have been identified. The similarity of irAEs to autoimmune disorders fuels the hypothesis that irAEs may be linked to susceptible genetic loci related to various autoimmune diseases. In this review, we extensively searched for susceptible loci associated with various autoimmune diseases, and pooled them in groups most likely to be associated with CPI-induced irAEs. These sets could be used in future research on predicting irAEs and guide physicians in a more refined and personal manner.

INTRODUCTION

Remarkable achievements in the treatment of once considered incurable cancers have been made since the introduction of immunotherapeutics. Immune checkpoint inhibitors (CPI), especially anti-PD-(L)1 antibodies, have improved survival in metastatic melanoma, lung cancer, renal cancer, urothelial cancer and advanced Hodgkin's lymphoma and promises to be effective in other cancers as well.[1–5]

Combining anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) with anti-programmed cell death protein (PD-1) can increase response rates and progression-free survival (PFS) further, for example, the combination of ipilimumab plus nivolumab demonstrated a median PFS of 11.5 months vs 2.9 months and 6.9 months for ipilimumab or nivolumab alone in patients with advanced melanoma.[4] Other combinations, for example, nivolumab plus relatlimab (anti-lymphocyte activation gene 3 (LAG-3)), can overcome resistance to anti-PD-1 monotherapy.[6] Moving combination immunotherapy to earlier stages of disease seems to increase the response rate further, but at cost of higher incidence of severe toxicities.[7–10]

Severe adverse events (AE) from CPI are observed in about 15% of patients treated with anti-PD-1/PD-L1, 20%–30% with ipilimumab and in up to 60% in ipilimumab/nivolumab combination therapy in late-stage disease.[4 11–17] These AEs, called immune-related (ir)AEs or AEs of special interest, closely resemble autoimmune diseases (AID), but usually lack the chronicity of AID. AEs can be found in any organ or tissue of the body, usually develop within the first 3 months of treatment with CPI (ranging from days after start-up to 1 year after cessation of therapy) and require prompt management.[18]

The most prevalent irAEs are gastrointestinal, skin, endocrine or liver toxicities, while myositis, arthritis, sarcoidosis, neuropathies and nephritis are less frequently reported.[12 13 19–21] Severe irAEs can be managed with immune-modulatory medications, such as steroids, anti-tumour necrosis factor-alpha (TNF-α) antibody (eg, infliximab or inflectra), mycophenolate mofetil or calcineurin inhibitors like tacrolimus and cyclosporine.[22] While reversal in the majority of cases will be achieved, long-term hormonal substitution therapy for endocrine disorders occurs regularly.[15]

As only a subset of patients treated with CPI develop severe AEs, it would be advantageous to upfront identify patients most likely to experience these toxicities. To date,

however, no predictive biomarker has been identified to anticipate for treatment-related toxicities. The similarity to autoimmune disorders argues for a possible link to susceptible loci single nucleotide polymorphisms (SNP)/genetic alterations related to various AID, although acknowledging that treatment-induced irAEs and AID also differ in some aspects (time of onset, flare episodes). Genome-wide association studies (GWAS) have uncovered hundreds of risk loci for AID, although it remains to be elucidated how risk variants affect gene regulation and immune function.[23] Treatment with immune CPI antibodies in patients with pre-existing risk loci for AID could trigger an erroneous immune response that damage healthy tissues of these patients. In line with this idea, 55% of patients with AID experience an AID flare and/or severe irAEs on PD-1/PD-L1 targeting therapies, which is significantly more frequent than non-AID patients.[24] Thus, loci associated with AID likely play an important role for onset of irAE and should be examined in patients who receive CPI therapy.

In this review, we discuss which susceptible loci that are associated with various AID are potentially relevant for CPI treatment-induced irAEs. We provide an overview of reported irAEs, categorised according to affected organs. We focus on reported relevant immune-related susceptible loci possibly related to treatment-related autoimmune toxicity to facilitate plausible prediction. We anticipate that our comprehensive analysis might be the basis for large CPI-treated patient cohort correlative analyses.

METHODS

Data sources and searches

A broad search strategy was used using different databases: PubMed, Medline, Web of Science for literature and ImmunoBase search, OMIM, dbSNP NCBI, gene NCBI for genetic alterations and gene function information. The search was restricted to English language articles and published until January 2019.

Study selection

Relevant studies were selected by screening titles and abstracts, then by reviewing the full text and corresponding reference list. Important references were hand searched. Case reports and reviews of case reports describing irAEs in patients with melanoma (and to a fewer extent lung and kidney cancer) following treatment with anti-CTLA-4 and/or anti-PD-1 antibodies were included. Only the Food and Drug Administration (FDA)-approved CPI ipilimumab, pembrolizumab and nivolumab were included in this review and all case reports on non-FDA-approved CPI therapy were excluded.

Preferably, (meta-analysis of) GWAS with large study cohorts (>1000 patients) was selected to rapport susceptible loci for the different AIDs. However, if no large genetic studies were reported for the disease in question, genetic studies with smaller cohorts (50–1000 patients and very small cohorts <50 patients and single case studies) were included. Relevant studies were identified and are listed in the References section, and in the References section of the online supplementary file 1.

Supplementary material

See online supplementary file for used search terms.

irAEs and susceptible loci for AIDs

The clinical presentation of irAEs often resembles various AIDs and thus might be associated with susceptibility loci associated to AID. In table 1, we summarised the most common irAE categories (sorted by level of challenge to identify and treat) and the AIDs with corresponding symptoms including the known associated susceptibility loci. We highlight irAEs that cause permanent damage and can be life threatening, if not promptly recognised. In our opinion, these should include all reported neuropathies (Guillian-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), enteric neuropathy, myasthenia gravis (MG)), cardiomyopathies, most endocrinopathies (hypophysitis, type 1 diabetes mellitus (T1D), adrenalitis), and the dermatological diseases drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Subsequently, we will describe in detail the different irAE categories and current ideas about the pathophysiology of the individual correlating autoimmune phenomenon.

Autoimmune neuropathies

Autoimmune neuropathies can manifest acutely or chronically. A complex interaction between antigen-presenting cells, B-cells and different types of T-cells results in demyelination or axon loss. Different progressive neurological toxicities were reported following CPI treatment, resembling various autoimmune neuropathies.[25–31] Although the observed immune-mediated neuropathies remain rare (<3% of patients after treatment with ipilimumab[15 18]), these side effects can cause permanent damages and are potentially fatal.

There are several reported cases of GBS after or during treatment with CPI (online supplementary table 1). GBS is a potentially reversible, acute demyelinating polyneuropathy with a complex pathophysiology, in which infiltration of spinal nerve roots and peripheral nerves by macrophages, antibodies and T-cells contributes to neural damage. Immune activation by CPI therapy may brake peripheral tolerance to ganglioside-related epitopes in patients who already have predisposition factors for the development of GBS. Genes encoding macrophage mediators and polymorphisms in the Fcγ receptor were associated with severity (table 1; online supplemental table 1).

The development of CIDP on CPI is rare (table 1). It is most likely also CPI induced and less likely part of a paraneoplastic syndrome, since CIDP and malignant disease are only rarely seen concurrently.[32] CIDP

Table 1 Reported immune-related adverse events and possible associated genetic loci based on descriptions in autoimmune disease (AID). Most common immnue-related adverse event (irAE) categories, sorted by level of challenge to identify and to treat. Shared risk loci between AID are underlined

Reported immune-related adverse events	References	Possible susceptible loci based on autoimmune diseases (References)
Neuropathies		
Guillian-Barré syndrome (GBS)	25 31 33 93	*MMP-9*, *TNF-α*,[94] Fcγ receptors[95]
Chronic inflammatory demyelinating polyneuropathy (CIDP)	33 96	*HLA-Aw30*, *HLA-B8*, *HLA-Dw3*,[97–99] *HLA-DR2*,[100] *HLA-DRB1*13*,[101] *FCγRIIb*,[102] *SH2D2A*[103]
Enteric neuropathy	36 104 105	*RET*,[106] *GALNACT-2*, *RASGEF1A*,[107 108] *HLA-DQ* region,[109] between *LTA-α* and *TNF-α*,[110] *VIPR1*,[111] *IL-10*,[112] *IL-23R*,[113] *RAD21*,[114] *SGOL1*,[115] *MT-TL1*,[116] *TYMP*[117]
Myasthenia gravis (MG)	31 118–120	*CTLA-4*,[121 122] *HLA-DQA1*, *TNFRSF11A*,[121] *CHRNA1*, *AIRE*[122]
Multiple sclerosis (MS)	123	
Immune polyneuropathies, posterior reversible encephalopathy syndrome, aseptic meningitis, transverse myelitis and immune encephalitis	30 36 124	
(Cardio)myopathies and skeletal disease		
Rheumatoid arthritis (RA)	15 36 125 126	*MMEL1*, *PTPN22*, *IL-6R*, *DNASEIL3*, *CD5 ICAM-3*, *TYK2*[127 128]
Myopathies	15 36 126 129 130	*SLCO1B1*[131]
Myocarditis	4 12 130 132 133	*HLA-DR4*, *HLA-DR12*, *HLA-DR15*, *HLA-DPB*06:01*[134–136]
Pericarditis	137	
Cardiac arrest and Takotsubo cardiomyopathy	138	
Genitourinary diseases		
Nephritis	4 14 15 22 37 64 119 139 140	*FAN1*,[141] meta-analysis GWAS[142 143]
Vasculitis of uterine and ovarian vessels	144	
Endocrinopathies		
Hypophysitis	4 36 145 146	
Thyroid disorders	145–147	Immunochip project,[148 149] *PTPN22*, *CTLA-4*, *TSHR*, *MMEL1*, *LPP*, *BACH2*, IL-2RA[148]
Adrenalitis	36 145	*HLA-DR3*, *HLA-DQ2*, *HLA-DR4*, *HLA-DQ8*, *MICA*, *CTLA-4*, *PD-L1*, *PTPN22*, *CIITA*, *CLEC16A*, *CYP27B1*[150]
Type 1 diabetes mellitus	36 145 151	*PTPN22*, *CTLA-4*, *IL2RA*, *CLEC16A*, *IFIH1*, *IGF2*, *C12orf30*, *ERBB3*, *PTPN2*, *HLA-DQA1*[152]
Gastrointestinal diseases		
Colitis (inflammatory bowel disease (IBD); Crohn's disease (CD) and ulcerative colitis (UC))	12 15 36 40 146 147	*LRRK2*, *NOD2*, *HNF4A*, *IL-2RA*, *RTEL1-TNFRSF6B*, *CARD9*, *IFIH1*, *IKZF1*, *GPR35*, *NKX2-3*, *SMAD3*, *JAK2*, *IL-23R*, *PRDM1*[153]
Gastritis	44	[154–156]
Coeliac disease	39	
Hepatitis	4 14 63 64	HLA haplotypes,[157–160] *CARD10*, *SH2B3*[161]
Dermatological diseases		
Vitiligo	46 162 163	*TYR*, between *OCA2* and *HERC2* and *MC1R*, *IFIH1*, *CD80*, *CLNK*, *BACH2*, *SLA*, *CASP-7*, *CD44*, *IKZF4*, *SH2B3*, *TICAM1*, *TOB2*[164 165]
Lichenoid reactions	46 47 50	*TNF-α*, *IFN-γ* (in Northern Italian population)[166]
Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome	46 119	*HLA-B*58:01*, *HLA-B*57:01*[57 167]
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	36 46 119	*HLA-B*15:02*,[56 168] *HLA-A*31:01*,[58] *HLA-B*58:01*[59]

Continued

Table 1 Continued

Reported immune-related adverse events	References	Possible susceptible loci based on autoimmune diseases (References)
Psoriasis	36 169–171	*IFIH1*, *ERAP2*, *IL-12B*, *MICA*, *TYK2*[60]
Alopecia	172	[61]
Dermatitis	36	
Respiratory diseases		
Pneumonitis	15 36 63 64 146 147 173 174	*SP-C*,[175 176] *AIRE*,[177] *TERT*, *MUC5B*[178–180]
Haematological conditions		
Red cell aplasia	36 181	
Neutropenia	4 14 182	*FOXP3*,[183] chemotherapy-induced neutropenia associated with susceptible loci[184–186]
Acquired haemophilia A (AHA)	187	*HLA-DRB*16*, *HLA-DQB1*05:02*, *CTLA-4*[188]
Aplastic anaemia	189	*TNF-α*,[190] *HLA-A*02:01*, *HLA-A*02:06*, *HLA-A*31:01* and *HLA-B*40:02*,[191] *TERF1*, *TERF2*, *IL-23R*[192 193]
Disseminated intravascular coagulation	36	
Ophthalmological diseases		
Multifocal bilateral choroidal neovascularisation	194	*CFH*[195]
Graves' ophthalmology (GO)	36	*IL-1A*[196]
Optic neuropathy	96 197	
Vogt-Koyanagi-Harada (VKH) syndrome	198 199	*HLA-DRB1*04:05*, *IL-23R*, *ADO-ZNF365-EGR2*[200]
Systemic disease		
Sarcoidosis	36 46 201–207	*BTNL2*, *ANXA11*, *HLA-DRA*, *HLA-DRB5*, *HLA-DRB1*[208 209]
Systemic lupus erythematosus (SLE)	210	GWAS studies[211–213]

ADO, 2-Aminoethanethiol dioxygenase; AIRE, autoimmune regulator; ANXA11, annexin A11; BACH2, BTB domain and CNC homologue 2; BTNL2, butyrophilin-like 2; CARD9, caspase recruitment domain family member 9; CARD10, caspase recruitment domain family member 10; CASP-7, caspase-7; CFH, complement factor H; CHRNA1, cholinergic receptor nicotinic alpha 1 subunit; CIITA, class II major histocompatibility complex transactivator; CLEC16A, C-type lectin domain containing 16A; CLNK, cytokine-dependent haematopoietic cell linker; CTLA-4, cytotoxic T-lymphocyte associated protein 4; CYP27B1, cytochrome P450 family 27 subfamily B member 1; DNASEIL3, deoxyribonuclease 1-like 3; EGR2, early growth response 2; ERAP2, endoplasmic reticulum aminopeptidase 2; ERBB3, erb-b2 receptor tyrosine kinase 3; FAN1, Fanconi anaemia-associated nuclease 1; FOXP3, forkhead box P3; GALNACT-2, polypeptide N-acetylgalactosaminyltransferase 2; GPR35, G protein-coupled receptor 35; GWAS, genome-wide association studies; HERC2, HECT and RLD domain containing E3 ubiquitin protein ligase 2; HLA, human leucocyte antigen; HNF4A, hepatocyte nuclear factor 4 alpha; ICAM-3, intercellular adhesion molecule 3; IFIH1, interferon induced with helicase C domain 1; IFN-γ, interferon gamma; IGF2, insulin-like growth factor 2; IKZF1, IKAROS family zinc finger 1; IKZF4, IKAROS family zinc finger 4; IL-10, interleukin 10; IL-1A, interleukin-1A; IL-12B, interleukin 12B; IL-6R, interleukin 6 receptor; IL-23R, interleukin receptor 23; IL-2RA, interleukin 2 receptor subunit alpha; JAK2, Janus kinase 2; LPP, LIM domain containing preferred translocation partner in lipoma; LRRK2, leucine-rich repeat kinase 2; LTA-α, lymphotoxin alpha; MC1R, melanocortin 1 receptor; MICA, MHC class I polypeptide-related sequence A; MMEL1, membrane metalloendopeptidase-like 1; MMP-9, matric metallopeptidase 9; MTTL1, mitochondrially encoded tRNA leucine 1 (UUA/G); MUC5B, mucin 5B oligomeric mucus/gel forming; NKX2-3, NK2 homeobox 3; NOD2, nucleotide binding oligomerisation domain-containing 2; OCA2, OCA2 melanosomal transmembrane protein; PD-L1, programmed cell death 1 ligand 1; PTPN2, protein tyrosine phosphatase, non-receptor type 2; PTPN22, protein tyrosine phosphatase, non-receptor type 22; RAD21, RAD21 cohesin complex component; RASGEF1A, RasGEF domain family member 1A; RET, ret proto-oncogene; RTEL1, regulator of telomere elongation helicase 1; SGOL1, shugoshin-like 1; SH2B3, SH2B adaptor protein 3; SH2D2A, SH2 domain-containing 2A; SLA, Src-like adaptor; SLCO1B1, solute carrier organic anion transporter family member 1B1; SMAD3, SMAD family member 3; SP-C, surfactant protein C; TERF1, telomeric repeat binding factor 1; TERF2, telomeric repeat binding factor 2; TERT, telomerase reverse transcriptase; TICAM1, toll-like receptor adaptor molecule 1; TNF-α, tumour necrosis factor alpha; TNFRSF11A, TNF receptor superfamily member 11a; TNFRSF6B, TNF receptor superfamily member 6b; TOB2, transducer of ERBB2, 2; TSHR, thyroid-stimulating hormone receptor; TYK2, tyrosine kinase 2; TYMP, thymidine phosphorylase; TYR, tyrosinase; VIPR1, vasoactive intestinal peptide receptor 1; ZNF365, zinc finger protein 365; pRDM1, PR/SET domain 1.

is characterised by demyelination, remyelination, interstitial oedema and endoneurial inflammatory cell infiltrates.[33] Genetic variation in immune-related genes could contribute to acquiring disease after trigger of CPI (table 1; online supplemental table 1).

Enteric neuropathy following treatment with anti-CTLA-4 and/or anti-PD-1 has been described in few patients, but is usually severe (table 1).[15] This degenerative neuromuscular condition of the digestive system results in variable degrees of impaired motility of the digestive tract. Enteric neuropathies are classified depending on where the symptoms present along the gastrointestinal tract. Susceptible loci are reported for each location (online supplementary table 1).[34 35] The molecular genetic basis of Hirschsprung disease, in which the rectosigmoid is mostly affected, is the most

intensively investigated enteric neuropathy. The disease is considered to be polygenic or multifactorial in origin; however, a variety of point mutations in the *RET* gene (a transmembrane receptor tyrosine kinase) are considered to be a major contributing factor (table 1; online supplemental table 1).

The development of muscle weakness symptoms (fatigable muscle weakness in the limbs with bulbar dysfunction) that are in line with MG has been described after receiving CPI therapy (table 1). Muscle weakness is caused by antibodies that block or destroy nicotinic acetylcholine receptors at the junction between nerves and muscles. GWAS identified variations in genes known to affect immune functions, as well as genes that reflect their unique role in pathology that contribute to susceptibility to neuroimmunological conditions (online supplementary table 1). In particular, the polymorphism for *CTLA-4* is of interest, since this leads to ineffective transcription of the *CTLA-4* gene, suggesting that it plays a central role in generating abnormal immune response that results in neuromuscular junction dysfunction.

Autoimmune (cardio)myopathies and skeletal disease

Cases of cardiac and musculoskeletal AEs following CPI treatment are increasingly reported. Musculoskeletal pain and stiffness are the most common AEs reported, but higher grade toxicity occurs infrequently. Severe events include polyarthritis, myositis, rhabdomyolysis, pericarditis and Takotsubo-like syndrome.[36]

A common irAE of CPI is arthralgia (combination CPI therapy: 11%).[4] Less common but more severe event is polyarticular inflammatory arthritis (any grade: 0%–2%),[15] characterised by inflammation of the joints (table 1). Rheumatoid arthritis (RA) is a common archetypal AID, in which GWAS identified 46 risk loci in genes of known immune function, both specific for RA or shared with other AID (table 1). Bioinformatic analyses generated potential causal SNPs at seven loci (online supplementary table 2; table 1). Other documented risk loci could also be of potential relevance to explain checkpoint-blocking treatment-related AEs.

Manifestations of myopathies have been described (any grade: <1%),[36] including (poly)myositis, myalgia, rhabdomyolysis, polymyalgia rheumatic/giant cell arteritis and autoimmune inflammatory myopathy (table 1). Autoimmune myopathies encompass a group of individual (rare) diseases characterised by the presence of muscle inflammatory infiltrate resulting in progressive muscle weakness. Pathophysiological knowledge is limited, and no genetic alterations have (yet) been established for autoimmune myopathy (online supplementary table 2; table 1).

Cardiac side effects have been recently described after CPI therapy (grade 3/4: 1%–2%),[15] including (fatal) myocarditis, pericarditis, cardiac arrest and Takotsubo cardiomyopathy (table 1). Immune mechanisms in heart diseases are complex, in which both humoral and cellular immunity are involved, but the course of autoimmune-mediated cardiac disorder is often not completely understood. Genetic predispositioning factors associated with autoimmune myocarditis are polymorphisms in MHC genes (online supplementary table 2; table 1).

Autoimmune genitourinary diseases

CPI-induced irAE affecting the genitourinary system has been described. Most of the reported irAEs affect the urinary system (0%–4%).[37] When these are not treated early on, persistent (severe) damage may develop (table 1).

(Interstitial) nephritis is a common cause of renal toxicity. The pathogenesis of nephritis is complex and largely unknown. The role of autoimmune mechanisms is not well understood, and genetic predisposition factors are scarce. Multiple genetic linkage studies have provided evidence for a genetic component to renal failure, which include loci affecting renal function and creatinine production and secretion, and importantly, not encoding for immunoregulatory proteins (table 1). Since these loci are reported for a wide range of kidney diseases (which seem not to be immune related), most not corresponding with CPI-induced renal toxicities, we consider these loci of low importance for CPI.

Autoimmune endocrinopathies

Endocrine toxicities from CPI therapy are well-recognised irAEs (approximately 10% of patients). These include hypophysitis, hypothyroidism, hyperthyroidism and adrenal insufficiency. If not promptly recognised they can become life threatening, for example, Addison crisis (table 1), but can normally be managed easily with lifelong hormonal substitution therapy, beta-blockers or strumazol.[22]

Pituitary inflammation, or hypophysitis, is a frequently reported endocrine toxicity, causing hormonal dysfunction (combination CPI therapy: 8%) (table 1).[15] Immune-related hypophysitis is often presented with non-specific symptoms such as nausea, headache, fatigue and vision change caused by swelling of the pituitary gland (table 1). To date, no data are available associating autoimmune hypophysitis to susceptible genes.

Additionally, both hyperthyroidism (combination CPI therapy: 10%) and hypothyroidisms (combination CPI therapy: 15%) have been described.[15] Hyperthyroidism often turns into hypothyroidism after a few weeks. It is observed preferentially after anti-PD-1 or anti-CTLA-4 plus anti-PD-1 (table 1). Environmental as well as genetic factors are associated with autoimmune thyroid disease (AITD). The most convincing evidence for susceptibility loci has been limited by the Immunochip project (table 1). The most relevant susceptibility loci affect the T-cell receptor signalling pathway (online supplementary table 3; table 1).

Other endocrine irAEs occurring following CPI therapy include primary adrenal insufficiency

(combination CPI therapy: 0.5%) (table 1).[25] A third of these reported cases were grade 3 or higher, and can be life threatening if not diagnosed promptly (Addison crisis). Several genes that confer susceptibility to autoimmune adrenalitis have been identified (online supplementary table 3; table 1).

The incidence for T1D was higher in patients who received combination therapy compared with patients who received monotherapy.[4 11] Preclinically, it has been demonstrated that blockade of the PD-1 axis induced diabetes in non-obese diabetic mice.[38] Approximately 50% of the cases of CPI treatment-induced T1D were indicated as grade 3 or higher, making this a rare, but relevant irAE to report susceptibility loci, since affected patients need lifelong insulin replacement therapy (table 1). The well-defined T1D is characterised by insulin deficiency resulting from an autoimmune destruction of the insulin-producing β-cells in the Langerhans islets. Different GWAS have revealed 57 genetic contributors to the pathogenesis of T1D. A meta-analysis combining evidence of different GWAS identified 10 susceptibility loci with convincing effect size, some of which gene regions overlap with other autoimmune endocrinopathies (*PTPN22*, *CTLA-4*, *IL2-RA* and *CLEC16A*) (online supplementary table 3; table 1).

Autoimmune gastrointestinal diseases

The most frequently identified irAEs involving the gastrointestinal tract are diarrhoea and colitis (depending on the clinical or endoscopic diagnosis). The incidence of diarrhoea at any grade was higher in those treated with ipilimumab (33%) compared with nivolumab (19%), and was highest in the combination ipilimumab-plus-nivolumab group (44%).[4] Grade 3 or 4 effects occurred in 9% for diarrhoea and 8% for colitis in the combination ipilimumab-plus-nivolumab group.[11] Other reported toxicities affecting the gastrointestinal tract include hepatitis (any grade: 30%, grade 3 or higher: 18.8%), gastritis and coeliac disease.[4 22 39 40] Inflammation of the intestine (colitis/enterocolitis) commonly leads to moderate to severe diarrhoea. Severe colitis is the most frequent reason for treatment discontinuation, can be life threatening, due to subsequent intestinal perforation or dehydration (table 1).

Well-defined autoimmune intestinal diseases include inflammatory bowel disease (IBD), classified as either Crohn's disease (CD) or ulcerative colitis (UC). Both disorders are characterised by chronic inflammation of the gastrointestinal tract, in which CD involves the total digestive tract, and UC involves the colon and rectum. A major difference between IBD and irAE colitis is its chronicity and slow improvement on steroids or TNF blockers. The aetiology of IBD is complex and arises as a result of the interaction of genetic and environmental factors. To date, genetic studies have identified 163 susceptibility loci for IBD. Approximately 30% are shared between CD and UC and more than 50% are associated with other AIDs. However, the genetic contribution to the pathogenesis is poorly understood and, in most cases, genetic alterations are thought to have a minor role. Recent mapping studies have used susceptibility loci to explain genetic heterogeneity across diverse populations and clinical subphenotypes.[41 42] Moreover, it is emerging that the value of genetic studies is defined by just single susceptibility genes, and to identify disease-relevant pathways (eg, barrier function, innate/adaptive immunity, metabolic pathways, autophagy) to understand the genetic architecture of complex disease such as IBD.[43] Although all reported risk loci may be of importance to explain CPI-induced autoimmune colitis, a few loci with greater than 95% certainty to be a single causal variant have been reported for IBD, UC and CD. These 18 susceptible loci associated with IBD, UC and CD are potentially of greater value in explaining treatment-induced intestinal toxicities after CPI (online supplementary table 4; table 1).

Gastritis, an inflammation of the lining of the stomach, is also reported on CPI therapy (table 1). One of the common causes of non-CPI gastritis is the infection with *Helicobacter pylori* (table 1). All reported SNPs for gastritis are related to an *H. pylori* infection, which is not frequently seen in the reported CPI treatment-induced gastritis.[44] Therefore, we consider these loci of less relevance.

Grade 3 or 4 immune-related hepatitis is among the most common identified high-grade irAEs (8.3% and 6.1%, respectively, in response to combination therapy) (table 1). Autoimmune hepatitis (AIH) is a disease with an unknown aetiology, where GWAS identified genetic variants that predispose individuals to AIH. Identified human leucocyte antigen (HLA) haplotypes, both class I and class II associated with AIH, are variable between geographic and ethnic populations (online supplementary table 4; table 1). Only two non-HLA loci have been identified as risk factors for AIH (online supplementary table 4), making it difficult to find a genetic component underlying AIH.

Autoimmune dermatological diseases

Dermatological toxicities are one of the most frequently reported toxicities on CPI, but often manageable due to early detection.[37 45–50] Some skin toxicities such as vitiligo are more prevalently observed in patients with advanced melanoma than in lung cancer and renal cancer.[3 51–53] The most common skin toxicities are lichenoid reactions, eczema, vitiligo, bullous pruritus and rash. These AEs occur more frequently when patients received combination therapy compared with monotherapy. In patients treated with combination therapy, 35.1% developed rash, 4.2% were high-grade (grade 3 or 4) and 33.2% developed pruritus, 1.9% were high-grade.[4] Other (rare) severe dermatological toxicities include SJS, TEN, psoriasis, alopecia and DRESS syndrome (table 1).

Vitiligo is a complex disease, in which an autoimmune response directed against epidermal melanocytes results in patched depigmentation. The development of vitiligo followed by CPI treatment may be explained by expansion of anti-Melan-A T-cells that are specific to an anti-melanoma immune response. Interestingly, vitiligo is associated with clinical benefit on immune CPI therapy (table 1). Previous linkage analyses and GWAS identified vitiligo susceptibility loci, in which a meta-analysis uncovered SNPs spanning 14 different gene regions encoding immunoregulatory proteins as well as pathology-specific proteins (online supplementary table 5; table 1).

Lichenoid reactions (including oral mucosal lesions), characterised by infiltration between the epidermis and dermis, have been described after administration of CPI (table 1). Genetic factors were only identified in oral lichen planus in a small study cohort (online supplementary table 5; table 1).

Dermatitis is a frequent AE developing after administration of CPI (table 1). Although GWAS for dermatitis showed significant association with genes of the innate/adaptive immune system, the reports of dermatitis after CPI were relatively mild and treatable.[54] Therefore, we consider these polymorphisms of irrelevance for biomarker analyses.

Another more severe skin toxicity is the DRESS syndrome, characterised by skin rash, fever, lymph node enlargement and internal organ involvement (table 1). Other drugs, such as anticonvulsants, allopurinol, minocycline, sulfasalazine and abacavir, have been described as potential inducers of the rare cases of DRESS syndrome.[55] Genetic predisposition for (drug-induced) DRESS syndrome was found to be associated with specific HLA groups in some ethic groups, for example, it seems to be more common in Asian populations than in other parts of the world (online supplementary table 5; table 1).

Cases of the life-threatening skin toxicities SJS and TEN were also reported after CPI (table 1). As observed for DRESS syndrome, SJS and TEN are also associated with many different drugs.[56–59] Both SJS and TEN are characterised by confluent epidermal necrosis, caused by autoimmune response which can be triggered by drugs of infections. Genetic risk factors for SJS and TEN are strongly associated with HLA alleles (table 1).

A few sporadic cases of psoriasis, a chronic, inflammatory disease, characterised by erythematous, scaling lesions, have been observed after administration of CPI (table 1). Pathogenesis of CPI-induced psoriasis remains speculative. A meta-analysis reported potential causal SNPs for significant loci, half of which encode regulators of innate host defence.[60] The most strongly associated SNPs include *IFIH1*, *ERAP2*, *IL-12B*, *MICA* and *TYK2* (online supplementary table 5), all overlapping with other AIDs, such as T1D, vitiligo, CD, adrenalitis, multiple sclerosis (MS) and RA.

Alopecia is a disease that involves immune-mediated destruction of the hair follicles, occurring in 1.0%–2.0% of CPI-treated patients (table 1). In total, 13 susceptibility loci for alopecia were identified[61] (table 1), many overlapping with other AIDs, such as T1D, CD, UC, RA, AITD, MS and systemic lupus erythematosus (SLE). However, hair regrowth on immunosuppressive treatment is a well-recognised feature of imunne-related alopecia (table 1).[62] Accordingly, we consider alopecia not serious enough to pre-evaluate individuals at risk before receiving CPI therapy.

Autoimmune respiratory diseases

Serious respiratory AEs occur on CPI treatment. These include pneumonitis and acute respiratory distress syndrome. Combination therapy was associated with the highest rate of pulmonary toxicity (table 1).

Pneumonitis is a rare (any grade: 5%–10%, grade 3/4: 2%[63 64]), but potentially serious irAE first described in patients with melanoma treated with CPI, but more often observed in patients with non-small cell lung cancer treated with anti-PD-1. Pneumonitis is a general term for inflammation of the lung tissue and is further classified in different subtypes. The subtype interstitial lung disease has been identified as a rare but potentially severe treatment-related irAE. Recent genomic studies associated different genetic alterations that predispose or cause interstitial pneumonitis (online supplementary table 6; table 1).

Autoimmune haematological conditions

Treatment with CPI can cause haematological AEs, although rarely. The development of CPI-induced haematological diseases includes thrombocytopenia, aplastic anaemia, neutropenia, red blood cell aplasia, acquired haemophilia A (AHA) and disseminated intravascular coagulopathy (table 1).

Development of immune-mediated red cell aplasia, which is a type of anaemia affecting the erythropoietic precursor cells, occurred in patients treated with CPI (table 1). Anaemia has been restored in the majority of patients on immunosuppression. Red cell aplasia is in most cases autoimmune mediated, initiated either by antibodies, natural killer cells or T-cells. Genetic factors that predispose individuals for immune-mediated red cell aplasia have not (yet) been reported.

CPI treatment-induced cases of aplastic anaemia are characterised by T-cell-mediated immune destruction of haematopoietic cell results in pancytopenia (and thrombocytopenia) (table 1). Bone marrow failure results in increased risk for complications such as haemorrhage, infection, organ dysfunction and death. Genetic alterations that are significantly associated with increased risk for aplastic anaemia include *TNF-α* and *HLA* alleles (online supplementary table 7; table 1).

Mild neutropenia is regularly reported during CPI treatment; however, grade 3 and 4 neutropenia is infrequent (table 1). Immune-mediated neutropenia, characterised

by antineutrophil antibodies, is one of the established causes for neutropenia. There are few genetic alterations for autoimmune neutropenia described (online supplementary table 7; table 1).

AHA is a rare autoimmune bleeding disorder with a high mortality rate. It arises as a result of the production of autoantibodies against clotting factor VII, which is predominantly drug induced (eg, by penicillin and interferon-α). CPI treatment-related AHA (grade 3 or 4) is rare (table 1). Genetic predisposition factors for AHA include HLA polymorphisms and SNPs in *CTLA-4* (online supplementary table 7; table 1).

Autoimmune ophthalmological diseases

CPI has been associated with eye inflammation, which can be manifested as uveitis, conjunctivitis, orbital inflammation, Vogt-Koyanagi-Harada (VKH) syndrome, Graves' ophthalmology (GO), choroidal neovascularisation and optic neuropathy. The incidence of these ophthalmological diseases is less than 1%, and for most cases treatment with topical or systemic corticosteroids was effective.[36 65–67] The more severe adverse ophthalmological malignancies co-occurred with several other irAEs. Although the occurrence of these severe side effects is rare, we consider conditions that potentially result in vision loss of importance, hence we report potential risk loci (table 1).

A case of multifocal bilateral choroidal neovascularisation in a patient on ipilimumab was described (table 1). Choroidal neovascularisation is characterised by aberrant choroidal vessel formation in the eye and can cause vision loss by way of haemorrhage or retinal oedema. There have been no susceptible loci for choroidal neovascularisation identified up to date; however, choroidal neovascularisation is a form of age-related macular degeneration, in which polymorphisms in *CFH* are strongly associated, suggestive to be of relevance in choroidal neovascularisation as well (online supplementary table 8; table 1).

GO, generally occurring in patients in Graves' disease and hyperthyroidism, is an autoimmune inflammatory disorder which affects ocular and orbital tissues. Various associations between gene polymorphisms and GO have been established, mostly in interleukin (IL)-related genes. A meta-analysis confirmed only one polymorphism in *IL-1A* to be significantly associated (table 1; online supplemental table 8).

The uveomeningitic syndrome VKH has been associated with CPI therapy, although it occurs rarely (table 1). VKH is characterised by a systemic granulomatous autoimmune response that targets melanocyte-rich tissues, affecting the eye, inner ear, meninges, skin and hair. Several studies have demonstrated that HLA polymorphisms and two loci (*IL-23R* and the mRNA expression of *ADO-ZNF365-EGR2*) were associated with development of VKH syndrome in several (Asian) populations (online supplementary table 8; table 1).

Systemic AIDs

Defined systemic diseases occurred also on CPI treatment, which include diseases that affect a number of organs or tissues, some of which have been described above (eg, MG, coeliac disease, UC, CD, RA). Other reported CPI-induced systemic diseases, potentially severe, include sarcoidosis and SLE.[15 36]

CPI-induced sarcoidosis may complicate treatment continuation because enlarged lymph nodes might be misdiagnosed as disease progression. Sarcoidosis is an inflammatory disease, associated with granulomas in affected organs, most often in the lymph nodes. Any organ can be affected, and cases of lung, cutaneous, muscular and neurological sarcoidosis have been reported after administration of CPI (table 1). The aetiology is largely unknown, although presumably an aberrant T-cell immune response leads to the formation of granulomas. GWAS have linked different susceptibility loci to sarcoidosis (online supplementary table 9; table 1).

Another well-defined systemic disease is SLE, an AID that is characterised by autoantibodies, most commonly antinuclear antibodies, affecting various body tissues. Only one case of lupus nephritis was described so far in a patient who received monotherapy of ipilimumab, in parallel with an immune complex-mediated kidney injury. Despite the fact that GWAS studies have identified 47 susceptibility loci for SLE (table 1), the number of reported cases of SLE is too low.

DISCUSSION

CPI (combinations) are becoming more and more standard therapies in stage IV melanoma, lung cancer, renal cell cancer and bladder cancer. They are currently tested in other cancer types, and in (neo)adjuvant settings in earlier stage cancers. Moving these effective therapies towards adjuvant and neoadjuvant approaches in stage III disease in a curative setting makes the need for biomarkers for response and severe AEs even more important.[7 68] Unfortunately, there are currently no reliable biomarkers to predict occurrence of severe irAEs in response to CPI therapy. This urged us to write this review about several susceptibility loci identified for various AIDs which might also be relevant for irAEs, and could be a basis for correlative studies in CPI patient cohorts.

The development of high-throughput sequencing technologies has driven the discovery of more than 300 susceptibility loci for AID. In this review, we selected, in our view, the most important susceptible loci that potentially can predict treatment-induced irAEs (sorted by level of challenge to identify and treat). Multiple reported risk loci are shared between AID (which are underlined in table 1), and are known to affect immune functions, such as antigen presentation, cytokine signalling, NF-κβ transcriptional regulation and T-cell activation/inhibition. Other genes are specific for a certain AID and reflect their role in their unique pathology.[23]

Previous studies discovered that some susceptible loci are known to contribute more significantly to AID than other loci, which is explained by their effect size.[23 69] Here, we considered reported genes that were proven to contribute more significantly to autoimmune susceptibility than other reported genes of highest importance. One of the previously reported susceptibility loci with large effect size is the HLA locus in T1D, in which 30% of disease liability is attributed to the HLA locus, compared with 9% for other loci discovered across the rest of the genome with GWAS.[70 71] Another previously reported susceptibility locus with large effect size, which was identified by linkage analysis, is *NOD2* for CD (increasing risk to develop CD 20 to 40-fold when carrying mutations in both *NOD2* alleles).[72 73] In addition, candidate gene studies revealed several key discoveries, in which variants in *PTPN22* and *CTLA-4* (both also reported in this review) were most notable. *PTPN22* was shown to be associated with T1D (OR 2.31), RA (present in approximately 28% of the RA population and in 17% of unaffected population) and Graves' disease (present in approximately 14% of the Graves' disease population and in 8% of unaffected population).[74–77] *CTLA-4* was shown to be associated with T1D (OR 1.79), RA (OR 1.23) and alopecia (OR 1.44).[78–80] However, for many other genes identified by GWAS their contribution to autoimmunity remains to be examined, potentially having small effect size.[23] This makes it more difficult to report potential susceptibility loci that are implicated to be of highest importance to predict irAEs. Therefore, we suggest that reported risk loci with largest effect size should be assessed in order to determine their relevance as a predictive biomarker for (organ-specific) toxicity.

We propose to prioritise on irAEs that cause permanent damage and can be life threatening, as a high chance on such irAEs might alter the physicians' decision to not treat with CPI combinations. Although the reported cases for some of these serious irAEs (neuropathies, cardiomyopathies, nephritis) are less frequent, the given anticipated increase in the use of (combination) CPI to treat cancer will result in a rise in the number of reported cases over the coming years. Moreover, these therapies move towards adjuvant and neoadjuvant approaches in stage III disease with the intent to cure patients, which makes reduction in irreversible (severe) irAEs even more important. Therefore, clinical strategies should be developed to predict these toxicities, in which the proposed susceptible loci for AID could potentially serve as biomarkers for these serious irAEs.

Understanding the various immunological and non-immunological parameters associated with efficacy and toxicity of CPI, as well as other (promising) immunotherapies, will improve our treatment decision-making in a more refined and personalised manner. The 'Cancer Immunogram' we developed does not take the occurrence of (severe) AEs into account.[81] In order to implicate the likelihood of AEs to occur, predictive biomarkers are urgently required.

The recognition of risk factors would assist in identifying patients who are not optimally fit for CPI therapy, in whom use of alternative schedules or drugs would be potentially advantageous to reduce toxicities. Adjustment of dose of anti-CTLA-4 in patients at risk for severe irAEs is one possibility to reduce immune-related toxicities. Currently, there are studies in stage IV and stage III melanoma underway testing alternative combination schemes with the aim to reduce toxicity while preserving efficacy.[82 83] In addition, poor candidates for CPI therapy may benefit from additional surveillance and prompt aggressive treatment when AEs occur, or even prophylactic treatment with other immune-modulatory medications, which are not T-cell inhibitory.[84–86]

One could argue that treatment-induced irAEs may be related to AID, but differences in pathology of irAEs and AID are undeniable, such as flare episodes (not chronic vs chronic disease), the time to onset, which is weeks for treatment-related irAE, in contrast to autoimmune which usually develops more slowly.[37] These differences may also affect the chance that identified susceptible loci for AID have a predictive value for treatment-related toxicities. Nevertheless, we hypothesise that the environmental component, in this case CPI therapy, may trigger underlying inflammatory disease in genetic predisposed individuals, resulting in a more rapid onset of autoimmune-like symptoms. Moreover, response to treatment of CPI-related irAEs and AID is quite similar, such as susceptibility to corticosteroids and secondary immune-modulating agents, such as TNF-(R)-blocking agents.

Moreover, polymorphisms of *PD-1* and *CTLA-4* are associated with various autoimmune conditions (T1D, thyroiditis, Graves' disease, coeliac disease, SLE, RA) to which the observed treatment-related irAEs clearly share clinical features,[87] especially (inherited) changes in *CTLA-4* expression and susceptibility for developing AID.[88] Treatment with anti-CTLA-4 and/or anti-PD-1 antibodies prevents their regulation of peripheral immunological tolerance mechanism, which potentially could have a similar effect as changed expression in genetic polymorphism-associated AID. A better knowledge of the biology and ancillary genomics of the development of irAEs may provide more conclusive insight whether irAEs occur as a consequence of the patient's immunological profile (eg, polymorphisms or HLA status).

Altogether, the recognition of potential risk factors to identify predisposed individuals for CPI treatment-induced toxicities is desired, because the number of patients affected by irAEs will most certainly increase in the following years as a result of more patients being exposed to immune CPI (more indications and adjuvant treatment indications). First, we foresee an increase in combination immunotherapy as the standard of care resulting in more reported severe treatment-induced toxicities.[4] Furthermore, combination of established CPI with drugs targeting other related inhibitory immune checkpoints, including LAG-3, V-type immunoglobulin

domain-containing suppressor of T-cell activation, B and T-lymphocyte attenuator and T-cell immunoglobulin-mucin domain 3,[89–92] or agonistic antibodies targeting co-stimulatory molecules such as OX-40, CD27, CD28, CD137 and glucocorticoid-induced TNF-related protein,[89–92] may result in more irAEs. Therefore, biomarkers that predict immune CPI treatment-induced toxicities will remain of high value, in which AID-associated susceptibility loci are potentially good candidates warranting further investigation.

CONCLUSION

In spite of the beneficial effect of immune CPI therapy in patients with cancer, continuation of its use can be restricted by increased irAEs. As the indications for CPI are extending almost monthly, and we will soon move CPI to (neo)adjuvant settings, the number of patients experiencing irAEs will increase steadily. Incorporation of new predictive biomarkers that could exclude poor candidates (patients who are not responding and have high chance of severe toxicities) for this novel therapeutic modality would be of high value, especially since CPI therapy in stage III disease is moving towards a curative setting. The susceptible loci reported in this review could potentially function as a tool to identify predisposed individuals who experience (severe) irAEs in response to CPI therapy. Initially one needs to focus on loci with large effect size to establish reliably correlations with irAEs. For this, multinational initiative will be required collecting data from thousands of patients treated with CPIs.

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