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Facts and hopes in prediction, diagnosis, and treatment of immune-related adverse events

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Abstract

Over the past decade, the use of immune checkpoint inhibitors (ICIs) has expanded across a wide spectrum of oncology indications. Immune-related adverse events (irAEs) from ICIs represent a significant source of morbidity, and in rare instances, can lead to treatment-related mortality. There are significant opportunities to better identify patients at increased risk for immune-related toxicity, diagnose irAEs more accurately and earlier in their course, and develop more individualized therapeutic strategies once complications arise. Clinical characteristics, germline and somatic genetic features, microbiome composition, and circulating biomarkers have all been associated with higher risk of developing irAEs in retrospective series. Many of these data suggest that both anti-tumor and anti-host ICI-associated immune reactions may be driven by common features of either the tumor or the patient's pre-existing immune milieu. While irAE diagnosis is currently based on clinical history, exclusion of alternative etiologies, and sometimes pathologic confirmation, novel blood-based and radiographic assays are in development to identify these complications more precisely. Anecdotal reports and small case series have highlighted the potential role of targeted immunomodulatory agents to treat irAEs, though further prospective investigation is needed to evaluate more rigorously their use in these settings. In this review, we highlight the current state of knowledge about predicting, diagnosing, and treating irAEs with a translational focus and discuss emerging strategies which aim to improve each of these domains.

Introduction

Since the initial regulatory approval of the first anti-CTLA-4 antibody ipilimumab for metastatic melanoma in 2011,(1) the use of additional immune checkpoint inhibitors (ICIs) including nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, dostarlimab, and cemiplimab, has expanded across a wide spectrum of oncology indications.(2) Treatment-associated immune-related adverse events (irAEs) from ICIs represent a significant source of morbidity. IrAEs can affect any organ system, though the gastrointestinal tract, endocrine glands, skin, and liver are most commonly affected.(3) While most irAEs can be successfully treated with steroids and other immunomodulatory agents, rare, severe, irAEs such as myocarditis have been associated with mortality rates

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as high as 24%.(4) Severe irAEs occur more frequently when ICIs are combined; trials of the combination of nivolumab and ipilimumab in melanoma, renal cell carcinoma, and non-small cell lung cancer (NSCLC) have reported Grade 3-4 irAEs in 32-59% of patients.(5–7) The rate of severe irAEs is lower with single-agent blockade of programmed cell death-1 (PD-1) or programmed death ligand-1 (PD-L1), with a recent meta-analysis identifying Grade 3-4 irAEs in 14% of 20,128 patients treated with PD-1/PD-L1 monotherapy across 125 trials.(8) Interestingly, emerging combinations of PD-1/PD-L1 inhibitors with agents targeting novel checkpoints (e.g. LAG3, TIGIT) do not appear to cause the same rates of immune-related toxicity as combination PD-1 and CTLA-4 blockade, (9,10), though rates of irAEs are still higher than with PD-1 monotherapy.

As the administration of ICIs in routine clinical practice continues to increase, improved management of associated toxicities has major implications for patient outcomes. There are significant opportunities to better identify patients at increased risk for immune-related toxicity, diagnose irAEs more accurately and earlier in their course, and develop more individualized therapeutic strategies once complications arise. Other consensus reviews discuss recommendations for specific irAE management, including those from the American Society of Clinical Oncology (ASCO),(11) National Comprehensive Cancer Network (NCCN),(12) Society for Immunotherapy of Cancer (SITC),(13) and European Society for Medical Oncology (ESMO).(14) As such, we highlight the current state of knowledge about predicting, diagnosing, and treating irAEs with a translational focus and discuss emerging strategies which aim to improve each of these domains.

Prediction of irAE development in high-risk patients

Immune-related adverse events affect patients in markedly heterogeneous ways. Methods to identify patients who may be at greatest risk for developing irAEs are actively being investigated. Several clinical parameters as well as exploratory biomarkers have been associated with greater toxicity, though none has yet been prospectively validated. Published studies on factors related to prediction of irAEs are summarized in Table 1.

Pre-existing autoimmune disease

Since irAEs represent the aberrant activation of the immune system against normal non-malignant tissues, patients with underlying autoimmune disease have been identified as potentially being at greater risk of developing irAEs. As in unselected populations, rates of irAEs among patients with autoimmune disease, are higher with combined anti-CTLA-4/PD-1 combination therapy and anti-CTLA-4 monotherapy than with anti-PD-1 monotherapy.(15) Some irAEs in patients with autoimmune disease affect the organs previously involved in their underlying autoimmune disorder. Retrospective analyses of patients with autoimmune diseases treated with commercially available ICIs have identified rates of autoimmune disease flare ranging from 28 to 60%.(16,17) In a retrospective multicenter analysis of 102 patients with underlying inflammatory bowel disease (IBD) treated with ICIs, gastrointestinal adverse events occurred in 41% of these patients compared to 11% of patients treated at the same centers without histories of IBD.(18) irAEs can also affect new organ sites that were unaffected by autoimmunity prior to ICI therapy.

A systematic review of 123 patients with a variety of autoimmune diseases treated with CTLA-4 and/or PD-1 blockade demonstrated exacerbations of existing autoimmune diseases in 41% of patients, de novo irAEs in 25% of patients, and both in 9% of patients.(19) A separate retrospective analysis of 470 patients treated with ICIs identified an association between both personal history (adjusted odds ratio (OR) 2.57, $p = 0.001$) and family history (adjusted OR 5.98, $p < 0.001$) of autoimmune disease and the development of any irAE.(20)

An association between autoimmune disease and irAEs, however, has not been universally identified in all published patient cohorts—a retrospective analysis of 417 patients treated with ICIs did not identify any association between underlying autoimmune disease and irAE incidence or severity.(21) In interpreting these conflicting data, it is important to consider whether patients with less severe manifestations of autoimmune disease or longer periods of quiescence may be more likely to be considered for ICI therapy in the standard-of care setting.

Mechanistically, recently identified germline genetic features have been suggestive of shared biological pathways between the development of irAEs and autoimmune disease. An exploratory sequencing study of 89 patients with melanoma that received ICIs identified 30 variants or single-nucleotide polymorphisms that were associated with an increased or decreased risk of developing irAEs; nine of the identified SNPs mapped to eight genes that have been implicated in autoimmune disease.(22) Germline inheritance of human leukocyte antigen (HLA) DRB1 shared epitope alleles are a known risk factor for the development of rheumatoid arthritis,(23) and rates of HLA-DRB1 shared epitope alleles were recently found to be higher in patients that developed ICI-related arthritis compared to healthy controls (62% v. 41%; OR 2.3, $p = 0.04$).(24) The HLA-DR4 allele has similarly been associated with ICI-induced type 1 diabetes.(25)

Circulating biomarkers have also suggested mechanistic links between autoimmune disease and irAEs. In a cohort study examining the incidence of irAEs in 137 patients with NSCLC treated with nivolumab or pembrolizumab monotherapy, pre-treatment autoantibodies (including antinuclear antibody, antithyroglobulin, and antithyroid peroxidase) and positive rheumatoid factor (>15 IU/mL) were associated with higher rates of irAEs ($p = 0.002$, $p = 0.006$, respectively).(26) In a separate cohort of 60 patients with melanoma treated with ipilimumab followed by PD-1 blockade, 7 of 11 (54.6%) patients with antithyroid antibodies after ipilimumab developed thyroid dysfunction with anti-PD1 therapy versus 7 of 49 (14.3%) patients without antibodies (OR, 9.96; 95% CI, 1.94–51.1).(27) These findings suggest that ICI administration may push a population of patients with sub-clinical autoimmunity toward clinically significant autoimmune events. Though PD-1 blockade is thought to exert its anti-cancer effect primarily though effector T cell activation, autoantibody-producing B cell populations may also express PD-1 and can be activated with PD-1 inhibitors.(28) Further investigation is needed to better elucidate the role of both B and T cell dependent autoimmunity in the development of irAEs. In addition to a history of autoimmune disease, sex(29) and body mass index (BMI)(30) have been identified as risk factors for the development of irAEs, though these associations have not been demonstrated consistently in other patient cohorts. (31,32).

Response to ICI therapy

Additionally, observational and translational data have suggested a potential association between tumor response to ICI and increased risk of developing irAEs. While an early analysis of patients with melanoma treated though the ipilimumab expanded access program did not identify a relationship between progression-free survival and irAE incidence,(33) several subsequent studies have linked radiographic tumor response with irAE incidence.(34) A meta-analysis of 7,936 patients with advanced solid tumors across 48 clinical trials treated with ICIs identified a correlation between the objective response rate (ORR) to nivolumab with the incidence of dermatologic ($p < 0.001$), gastrointestinal ($p = 0.006$), and endocrine ($P < 0.001$) irAEs, but not hepatic, pulmonary, and renal irAEs. In the same study, the ORR of combined nivolumab + ipilimumab correlated with incidence of skin ($p = 0.04$) and gastrointestinal irAEs ($p = 0.02$).(35)

Similarly, a pharmacoepidemiologic study of irAE reports across 18,706 patients in the FDA Adverse Events Reporting System (FAERS) receiving PD-1/PD-L1 checkpoint blockade showed a marginal association between irAE frequency and the ORR across tumor types ($Rs = 0.44$, $p = 0.049$).(36) This same analysis identified a bivariate model of lymphocyte cytosolic protein 1 (*LCP1*) and adenosine diphosphate dependent glucokinase (*ADPGK*) expression across tumors as predictive of irAE incidence ($Rs = 0.91$); both of these genes have been associated with T-cell activation in other contexts.(37,38) There are more limited available data linking irAE incidence to response or survival within a single disease entity; for example, in a population of 134 patients with NSCLC, Haratani et al. demonstrated irAEs within six weeks were positively associated with improved survival outcome, with hazard ratios of 0.525 ($p = 0.03$) for PFS and 0.282 (95% CI, 0.101 to 0.667; $P = .003$) for OS.(39) A similar association between ICI-related diarrhea and improved OS has also been reported.(40) Of note, the relationship between irAEs and clinical outcomes could be confounded by time-dependent biases (i.e., an irAE may appear to be associated with more favorable OS if the irAE takes time to develop, while patients who progress or die early may not have sufficient time to develop an irAE). Landmark analyses, such as those used by Haratani et al., aim to minimize these biases by using only irAEs documented in a fixed time period to distinguish clinical cohorts and limiting survival analysis to patients who are either alive (for OS analyses) or without progression (for PFS analyses) at the conclusion of that time period.

A number of tissue and circulating biomarkers recently associated with irAEs share similarities with biomarkers associated with tumor response to ICI therapy. Comparing multiple tumor types, higher tumor mutational burden(41) and a bivariate model of CD8+ T cells and T-cell receptor diversity have been associated with higher rates of irAEs.(36) Among a cohort of 470 patients with a variety of solid tumors treated with ICI therapy, higher baseline ALC, > 2.6 k/ul (adjusted OR: 4.30), absolute monocyte count > 0.29 k/ul (adjusted OR: 2.34) and platelet count > 145 k/ul (adjusted OR: 2.23) were also associated with a higher incidence of irAEs.(20)

Circulating cytokines and immune cells

The role of cytokines in ICI response and toxicity remains less well characterized, but some studies have linked pre-treatment cytokine levels with the development of irAEs. In a prospective series of 140 patients with metastatic melanoma treated with ipilimumab, low baseline interleukin (IL)-6 serum levels were associated with higher rates of irAEs (OR = 2.84, p = 0.007).(29) Conversely, higher pre-treatment serum IL-17 levels were associated with development of Grade 3+ colitis in 29 patients with melanoma treated with peri-operative ipilimumab (p = 0.02).(42) Lim et al integrated measurements of 11 pre-treatment and early-treatment cytokines (G-CSF, GM-CSF, fractalkine, FGF-2, IFNa2, IL12p70, IL1a, IL1B, IL1RA, IL2, and IL13) into a CYTOX score to distinguish patients with melanoma that experienced severe toxicity with PD-1 monotherapy or combined PD-1/CTLA-4 therapy. This score was then validated in a separate cohort of 49 patients with melanoma with area under the curve of 0.68 (pre-treatment; p = 0.037) and 0.70 (early treatment; p = 0.017).(43) Notably, a separate analysis of pre-treatment cytokines in 52 patients with melanoma that experienced irAEs—including eight of the cytokines included in the CYTOX score—did not discern patients that experienced Grade 1-2 irAEs from those with Grade 3-4 irAEs (i.e., severe toxicity).(44)

In addition to cytokines, ratios of circulating immune cells have also been associated with the development of irAEs. In a single-institutional study of 391 patients treated with pembrolizumab for a variety of oncologic indications, the risk of irAEs was significantly lower in patients that had a baseline neutrophil-to-lymphocyte ratio of 3 or greater compared to those with a ratio less than 3 (OR = 0.37, 95% CI 0.17–0.81, p = 0.012).(45) This association was also observed in a separate analysis of 184 patients with NSCLC treated with anti-PD-1 monotherapy.(46) Baseline circulating absolute eosinophils greater than 0.125×10^9 cells/L were also associated with higher rates of ICI-associated pneumonitis (27.7% v. 9.8%, p < 0.001) in a retrospective analysis of 300 patients with advanced NSCLC.(47)

Inherited genetic variants

There also has been interest in identifying germline genetic variants associated with irAEs, beyond those associated with autoimmune disease. The single-nucleotide polymorphism (SNP) *CTLA-4* -1661A>G was associated with an increased risk of endocrine irAEs in a cohort of 173 patients with melanoma treated with ipilimumab. (48) A similar analysis of 96 patients with NSCLC treated with nivolumab identified an association between the SNP *PDCD1* 804C>T and decreased incidence of irAEs (OR 0.4; 95% CI 0.2–1.0; p = 0.039), but this finding was not confirmed in a validation cohort.(49)

Microbiome & future directions

Recently, the role of the gut microbiome in anti-cancer immunity has emerged as an area of active research,(50) and the microbiome has similarly been implicated in the development of irAEs. Profiling of gut microbiota using 16s RNA sequencing demonstrated a significantly higher abundance of *Bacteroides intestinalis* (p = 0.009) *and Intestinibacter bartlettii* (p = 0.009) in patients with melanoma and toxicity from combined PD-1 and CTLA-4 blockade, compared to those who did not experience irAEs.(51) Interestingly, in a separately published

cohort of 34 melanoma patients treated with ipilimumab, higher stool abundance of the Bacteroidetes phylum (which includes *Bacteroides* as well as other commensal genera) was associated with resistance to ICI-induced colitis.(52)

All of the above analyses have generated hypotheses that have yet to be validated in prospective clinical trials, and no reported trial has adapted ICI therapy regimens based on pre-treatment risk of irAEs. An ongoing single-center prospective trial at University of Colorado Denver (NCT 03409016) is collecting blood samples at pre-treatment and three on-treatment time points to identify biomarkers that may predict ICI-related immunotherapy toxicity. There remains a significant opportunity to better discern which patients may be at highest risk for irAEs, and to individualize therapy based on this risk. Identification of highest-risk patients may be particularly important for trials of preventative interventions, as concomitant budesonide was ineffective for prevention of ipilimumab-associated colitis in a randomized controlled trial in an unselected population of patients with melanoma.(53) Several NIH-sponsored “Cancer Moonshot” U01 studies are prospectively assessing biomarkers of irAEs and exploring mitigation strategies for toxicities such as colitis and dermatitis.

Diagnosis of IrAEs

In addition to predicting which patients may be at highest risk for developing toxicity prior to initiating ICI therapy, early and accurate diagnosis of irAEs may provide clinicians opportunities to prevent hospitalizations or interruptions to anti-cancer therapy. From a research standpoint, standardized diagnostic criteria for irAEs may facilitate the aggregation of irAE data across clinical trials and real-world data.(54)

Recently published clinical practice guidelines from ASCO,(11) NCCN,(12) SITC,(13) and ESMO(14) provide broad diagnostic guidelines for a variety of irAE types. Generally, exclusion of alternate (namely infectious) etiologies is pursued in parallel with holding immunotherapy and/or beginning immunosuppression; pathologic confirmation is sometimes but not always obtained. To improve diagnostic accuracy, multiple groups have explored novel biomarkers that could eventually be translated to practice.

While pre-treatment biomarkers have been used to identify patients at highest risk for irAEs, analysis of on-treatment blood samples have identified dynamic changes in circulating immune parameters that coincide with or precede the development of irAEs. If validated in prospective patient cohorts, it is possible that these pre-treatment or on-treatment biomarkers could facilitate early diagnosis of irAEs before other clinical, laboratory, or radiographic findings appear. In a phase II study of 27 prostate cancer patients treated with ipilimumab and androgen deprivation therapy, clonal expansion of 55 or more T cell clones in the peripheral blood preceded development of Grade 2-3 ipilimumab-induced toxicities.(55) This finding was confirmed in a second cohort of 11 prostate cancer patients by the same authors. Changes in circulating cytokines, RNA transcripts, and autoantibodies have also been correlated with toxicity. Among 52 patients with melanoma treated with ipilimumab, IL-17 levels rose in patients with colitis and decreased with symptom resolution(56). Similarly, serum IL-6 levels were noted to rise in a small series of patients with malignant

melanoma and nivolumab-associated psoriasiform dermatitis, while it did not rise in patients who did not experience any irAEs.(57)

In a separate analysis of 360 patients treated with the anti-CTLA-4 antibody tremelimumab, an on-treatment RNA gene expression signature in peripheral blood was associated with treatment-associated diarrhea/colitis.(58) While most published reports do not correlate tissue-specific biomarkers with clinical patterns of ICI-related toxicity, Tahir et al. identified dynamic changes in anti-GNAL and anti-ITM2B antibodies (both reactive to antigens expressed in pituitary epithelium) in patients that experienced ICI-related hypophysitis as well as increases in anti-CD74 (expressed in lung and other tissues) in patients that experienced ICI-related pneumonitis.(59)

Ongoing translational trials will provide opportunity for further identification of potential diagnostic biomarkers. The Alliance A151804 trial (NCT04242095) opened in January 2020 and is prospectively collecting tissue, blood, and stool samples from patients experiencing Grade 3-4 adverse events. The Autoimmune Events Resulting from Systemic Modulation by Immuno-Therapy (AEROSMITH) trial led by the Parker Institute for Cancer Immunotherapy will collect longitudinal clinical and peripheral blood samples on up to 1,600 patients with a goal of elucidating mechanisms underlying irAE development. Additionally, a single-center study at Universitair Ziekenhuis Leuven in Belgium (NCT04807127) will prospectively apply single cell RNA- and TCR-sequencing on up to 5,000 single cells collected from broncheoalveolar lavage in patients experiencing pneumonitis.

In addition to circulating and tissue-based biomarkers, radiographic imaging also plays an important role in the noninvasive diagnosis of irAEs. Computerized tomography (CT) is commonly used to evaluate a variety of irAEs, and bowel wall thickening on CT was shown to be highly predictive (positive predictive value 96%) of biopsy-proven ICI-related colitis.(60) There are no pathognomonic radiographic findings that correlate with ICI-related pneumonitis--among 20 patients with solid tumors that developed ICI-related pneumonitis, a variety of radiographic patterns were identified but cryptogenic organizing pneumonia (COP) was most common.(61) A separate series of 27 patients treated at Memorial Sloan Kettering Cancer Center also demonstrated variable radiographic patterns, with ground glass opacities being the most common.(62)

In the future, advances in imaging technologies may improve the diagnosis of irAEs. For instance, a machine learning algorithm was able to distinguish between radiographic patterns of ICI and radiation pneumonitis (AUC 0.76)(63). Additionally, new positron emission tomography (PET) imaging modalities which image CD8+ T cells and granzyme B may be useful in non-invasively identifying organs affected by irAEs, as shown in a mouse model.(64,65)

Emerging Treatment Strategies for IrAEs

Current irAE treatment guidelines from ASCO, ESMO, SITC, and the NCCN(11–14) are largely based on expert opinion, as there has been limited prospective clinical investigation

in this setting to date. In many cases, management involves cessation of ICI therapy with or without initiation of topical, oral, or parenteral steroids depending on the organ involved and severity of the irAE. The best initial steroid dose and duration of steroid treatment have not been prospectively studied, raising questions as to whether the conventional one milligram per kilogram steroid dose for significant irAEs included in most consensus guidelines is really needed. There are also significant opportunities to develop novel therapies both in steroid-refractory settings (occurring, for example, in up to 18% of patients with ICI-related pneumonitis(66)) as well as with the goal to initially spare high doses of steroids, as systemic steroids themselves can be associated with many short- and long-term sequelae, and may negatively impact the efficacy of ICI therapy.(67,68)

Based on longstanding experience from the treatment of inflammatory bowel disease,(69) TNF-alpha blockade in steroid-refractory ICI-related enterocolitis is among the most well established targeted therapy in the management of irAEs, with 81% efficacy in steroid-refractory colitis observed in a recent meta-analysis.(70) The addition of the anti-TNF monoclonal antibody infliximab has also been associated with a shorter time to symptom resolution (3 v. 9 days, $p < 0.001$) despite higher-grade colitis in infliximab-treated patients.(71) However, when rigorously assessing response rates in a multicenter review of 127 patients with steroid-refractory ICI-related enterocolitis treated infliximab, only 51% of patients achieved steroid-free remission at 26 weeks. Though the primary endpoint in this study mandated complete resolution of diarrhea and may underrepresent the number of patients that derived clinical benefit, this result highlights the need for rigorous, prospective studies and exploration of novel targets for irAE treatment (72) (Figure 1).

More recently, investigators have studied the co-administration of TNF blockade in combination with immune checkpoint blockade. In a preclinical $Rag2^{-/-}Il2rg^{-/-}$mouse model adoptively transferred with human mononuclear cells, prophylactic TNF blockade with combined CTLA-4 and PD-1 blockade reduced colitis without compromising immune-mediated control of xenografted colon tumors.(73) A series of five patients treated at Massachusetts General Hospital with concurrent infliximab and ICI following ICI-related colitis facilitated steroid tapering without impairing tumor control.(74) Additionally, the ongoing TICIMEL trial (NCT03293784) is a Ph 1b study evaluating the safety and tolerability of treating metastatic melanoma with combination nivolumab and ipilimumab with either infliximab or certolizumab.(75) Early results of 14 treated patients showed treatment was well-tolerated, and all seven evaluable patients in the certolizumab arm had an objective radiographic response (four partial responses and three compete responses).(76) More mature data from this trial along with larger studies will be needed to determine if anti-TNF agents can reduce the incidence of irAEs without compromising anti-tumor outcomes, as was suggested by one registry study.(77)

Other targeted immunomodulatory agents have demonstrated efficacy in treating steroid-refractory ICI-related enterocolitis in published case reports and case series. The best studied is the anti-$\alpha_4\beta_7$ integrin monoclonal antibody vedolizumab,(78,79), with the notable advantage of being a gut-selective agent with theoretically less interference with systemic anti-tumor immune response. Other agents that have been effective in several reports include the JAK inhibitor tofacitinib,(80) and the anti-IL12/23 monoclonal antibody ustekinumab.

(81) While these reports are suggestive of a variety of treatment strategies for ICI-related enterocolitis, further prospective evaluation of these agents is needed to clarify their optimal use in routine clinical practice.

ICI-associated hepatic injury occurs less commonly than ICI-related colitis, but can be life-threatening in some cases. Mycophenolate mofetil has been shown to be safe and effective in the steroid-refractory setting.(82) Infliximab has not been tested in this setting due to concerns for hepatic toxicity, and is generally not used in patients with colitis and concomitant elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, one retrospective study of 56 patients treated with infliximab for a variety of steroid-refractory irAEs did not identify any significant differences in pre- and post-treatment AST and ALT. Also, one patient in this series was treated with infliximab for steroid-refractory ICI-associated hepatitis and was noted to have a complete recovery with no additional liver toxicity. (83)

There are more limited data available regarding novel immunomodulatory therapies for non-gastrointestinal irAEs. Though preclinical animal models for irAEs represent a major unmet research need, Wei and colleagues developed a genetic knockout mouse model that recapitulated ICI-related myocarditis and was ameliorated by treatment with abatacept. (84) Other reported data are predominantly clinical case series: in a single-institution series of 26 patients with steroid-refractory or steroid-resistant pneumonitis, addition of a second immunomodulatory agent (anti-TNF or mycophenolate) was associated with durable response in 10 patients (38%), including three with a complete response allowing for discontinuation of all immunosuppressants.(85) Treatment with the anti-IL-6 monoclonal antibody tocilizumab was associated with clinical benefit in 21 of 22 patients with advanced melanoma and a variety of irAEs (20 patients) or pre-existing autoimmune disorders (two patients). Circulating IL-6 was elevated in 12 of 13 patients with evaluable levels prior to tocilizumab administration.(86) A separate analysis of 34 patients treated with tocilizumab for nivolumab-associated steroid-refractory irAEs reported a clinical improvement in 27 of 34 evaluable patients (79%).(87)In a multicenter series of 285 patients with cutaneous irAEs, seven patients with steroid-refractory cutaneous irAEs were treated with biologics. (88) Three patients received the anti-CD20 antibody rituximab, two patients received the anti-IL-4 receptor alpha antibody dupilumab, one patient received ustekinumab, and one patient received the anti-IL-23a subunit antibody guselkumab. All seven patients experienced moderate to significant improvement in their cutaneous symptoms, though their presenting rashes were variable in morphology (e.g., bullous pemphigoid-like, psoriaform, eczematous). Three patients with radiographic tumor responses prior to adding a biologic maintained these responses after addition of the biologic. Successful treatment of pembrolizumab-induced psoriasiform dermatologic toxicity with the anti IL-17a monoclonal antibody has also been reported separately.(89)

More anecdotal data sets have highlighted the utility of targeted immunosuppressive agents in less common immune-related toxicities. These include tofacitinib and tocilizumab in ICI-associated arthritis,(90,91) infliximab in refractory ICI-related pericarditis,(92) and infliximab in ICI-associated acute tubular interstitial nephritis.(93)

Given the emerging role of the gut microbiome in immune-related toxicity, fecal microbiota transplant (FMT) has also been studied in the management of irAEs. Wang et al. reported the successful treatment of ICI-related colitis refractory to steroids, infliximab, and vedolizumab in two patients with FMT.(94) In both patients, there was a relative increase in CD4+ FoxP3+ T regulatory cells in comparison to other T cell lineages. There were also significant changes in the bacterial flora in both patients following FMT, but no single bacterial family was predominant in both instances. Several ongoing trials are prospectively assessing the role of FMT in treatment of ICI-related colitis (NCT04883762, NCT04038619, NCT03819296). In the ongoing Canadian PERFORM trial (NCT04163289), prophylactic FMT is being examined as tool to reduce the risk of colitis in patients with renal cell carcinoma receiving combination ipilimumab/nivolumab.

Given the rapid adoption of ICIs across multiple oncology indications, adept management of ICI-associated toxicity will have a major impact on a growing population of patients with cancer in the coming years. While the management of irAEs to date has not been based on randomized clinical trial data, clinical experiences to date have generated translational insights that may inform future advances in the prediction, diagnosis, and management of these adverse events.

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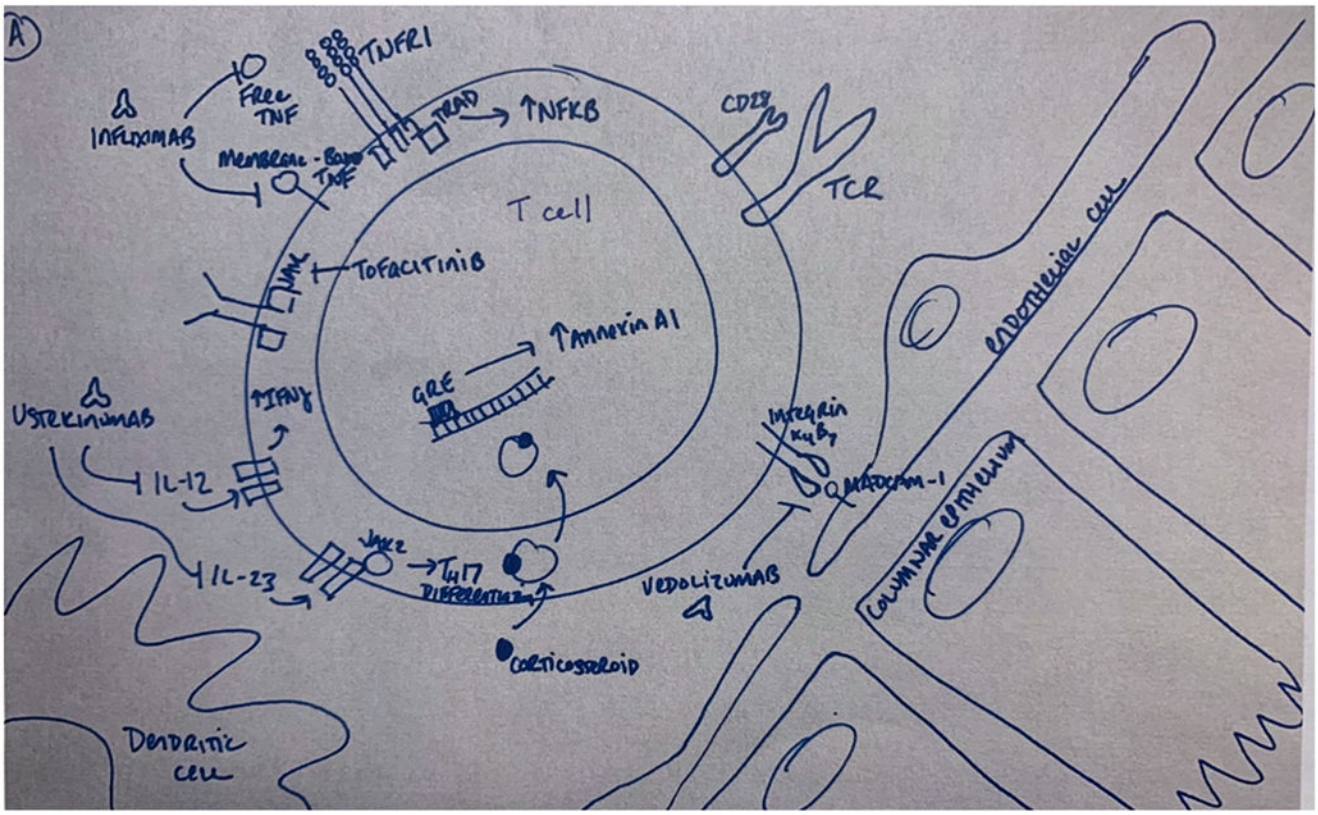

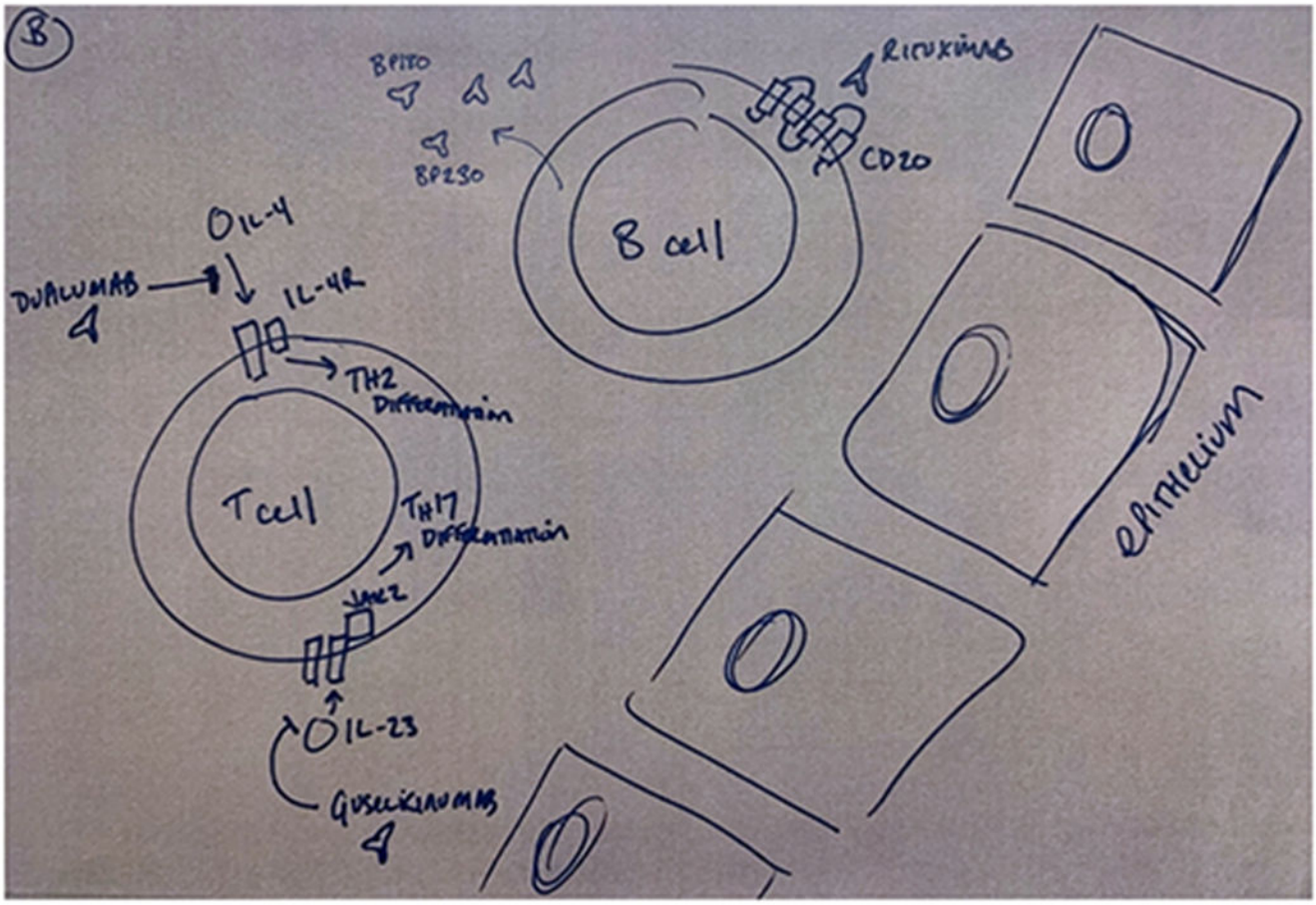

Figure 1.

Mechanisms of selected immunosuppressive agents reported in the treatment of gastrointestinal (A) and cutaneous (B) immune-related adverse events (irAEs). Monoclonal antibodies developed for other inflammatory indications have been used in the steroid-refractory setting. Examples include infliximab (anti-TNF), dupilimumab (anti-IL-4), guselkinumab (anti-IL-23), and ustekinumab (anti IL-12/23). Small molecules such as tofacitinib (anti-JAK1/3) have also been used.

Table 1.

Published studies on factors related to prediction of immune-related adverse events (irAEs).

Factors Associated with irAEs	Cited References
Pre-existing autoimmune disease	van der Kooij et al. (15), Fountzilas et al. (16), Alexander et al. (17), Abu-Sbeih et al. (18), Abdel-Wahab et al. (19), Michailidou et al. (20), Yeung et al. (21), Abdel-Wahab et al. (22), Cappelli et al. (24), Stamatouli et al. (25), Toi et al. (26), de Moel et al. (27)
Sex and body mass index	Valpione et al. (29), Guzman-Prado et al. (30), Shah et al. (31), Young et al. (32)
Response to ICI	Giacomo et al. (33), Das et al. (34), Xing et al. (35), Jing et al. (36), Haratani et al. (39), Wang et al. (40), Bomze et al. (41)
Circulating cytokines and immune cells	Valpione et al. (29), Tarhini et al. (42), Lim et al. (43), Tyan et al. (44), Eun et al. (45), Pavan et al. (46), Chu et al. (47)
Inherited genetic variants	Queirolo et al. (48), Bins et al. (49)
Microbiome	Andrews et al. (51), Dubin et al. (52)