PRIMEVIEW

IMMUNE-RELATED ADVERSE EVENTS OF ICIs

nature reviews disease primers

Immune checkpoint inhibitors (ICIs) — which are monoclonal antibodies against CTLA-4, PD-1 or PD-L1 — have transformed treatment of many cancer types. However, in some cases, these treatments are associated with immune-releated adverse events (irAEs).

EPIDEMIOLOGY

Onset of irAEs generally occurs between 2 and 16 weeks after ICI initiation, depending on the affected organ; however, some reports have noted onset within a few days of starting therapy and >1 year after completion. In general, PD-1 and PD-L1 inhibitors are tolerated better than CTLA-4 inhibitors, and ICI monotherapy is associated with fewer irAEs than PD-1/PD-L1 and CTLA-4 combination therapy.

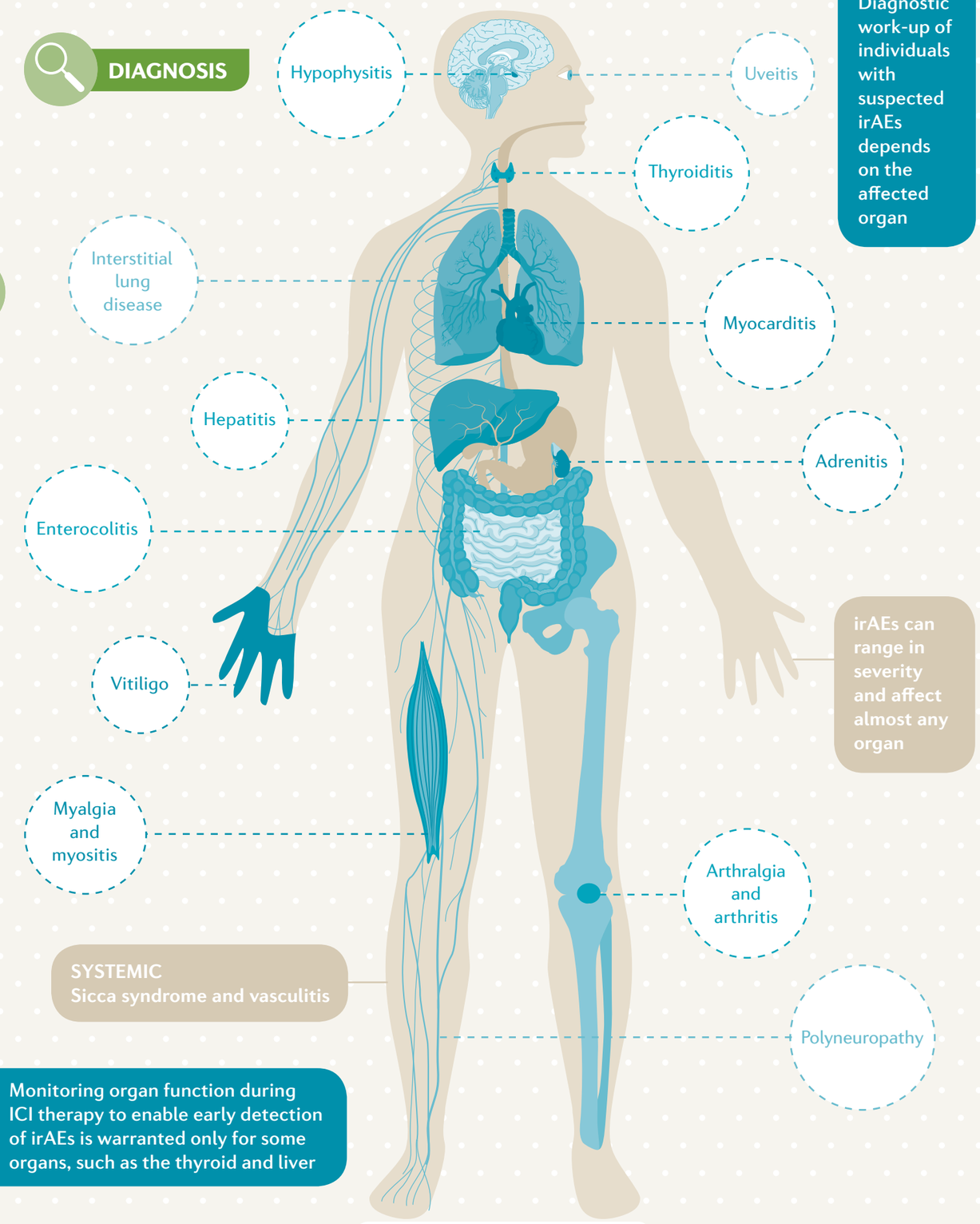
! Pre-existing autoimmune disease is a strong risk factor for developing irAEs

MECHANISMS

For CTLA-4 inhibitors, an imbalance in the ratio of regulatory T (T_{regs}) cells (which dampen the immune response) to type 17 T helper (T_H17) cells (which promote the immune response), autoantibody production and complement-mediated cellular damage have been suggested to contribute to irAE development. The mechanisms underlying PD-1/PD-L1 inhibitor-associated irAEs are less well understood but could be due to reduced T_{reg} cell numbers.

! ICIs targeting the CTLA-4 or PD-1/PD-L1 pathways facilitate T cell activation and survival, to induce an anti-tumour immune response

DIAGNOSIS



Monitoring organ function during ICI therapy to enable early detection of irAEs is warranted only for some organs, such as the thyroid and liver

Diagnostic work-up of individuals with suspected irAEs depends on the affected organ

irAEs can range in severity and affect almost any organ

MANAGEMENT

Treatment of irAEs depends on the affected organ and the severity of symptoms. ICIs should be halted following irAE diagnosis in most patients, except those with very mild symptoms. Glucocorticoids are the first-line therapy for most severe irAEs, following which non-steroidal synthetic immunosuppressive agents or intravenous immunoglobulin can be used if symptoms do not improve within 48–72 hours. Monoclonal antibody therapy against, for example, TNF or IL-6, or plasma exchange can be used for some irAEs. Deciding when to recommence ICI therapy to continue cancer treatment should be undertaken by a multidisciplinary team comprising organ specialists and oncologists. ICIs should be permanently discontinued in individuals with grade 3 myocarditis, pneumonitis and hepatitis, among others, and all grade 4 irAEs.

! Endocrine irAEs of all severities should be treated with hormone supplementation

OUTLOOK

Some studies have identified biomarkers associated with a higher risk of irAEs, such as pretreatment levels of serum autoantibodies. However, further studies are required before these autoantibodies can be used to guide management strategies in clinical practice. Moreover, as new ICIs or new combinations of therapies are approved, studies will be needed to characterize the associated risk, frequency and manifestations of irAEs.

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