When Steroids Fall Short:

Immunotherapy Challenges

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Introduction

- Immunotherapy enables the immune system to recognize, target and eliminate cancer cells.
- Sometimes this can cause side effects as a result of the immune system being over stimulated and mistakenly attacking healthy parts of the body
- Steroids work by suppressing the immune system to stop it from attacking your good cells and improving symptoms from side effects

Rachel S. Goodman, Douglas B. Johnson, Justin M. Balko; Corticosteroids and Cancer Immunotherapy. Clin Cancer Res 15 July 2023; 29 (14): 2580–2587. https://doi.org/10.1158/1078-0432.CCR-22-3181

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Common Side Effects

- Common side effects of immunotherapy include but are not exclusive to:
- Skin problems, ranging from rashes to the autoimmune disorders like endocrinopathies, hepatitis, and colitis, pneumonitis and others.
- People generally recover from these conditions after treatment with high doses of steroids.
- In rare occasions, they can develop more resistance to steroids.

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Epidemiology

Epidemiology

Immune-related adverse effects time of onset

- Most appear within 1-2 months after the start of treatment
- In some cases, they occur several months after starting or completing treatment

Checkpoint inhibitors

- The incidence of adverse events are seen with patients treated with anti-CTLA-4, anti-PD-1/PD-L1 monoclonal antibodies
- Patients treated with a combination of anti–CTLA-4 and anti–PD-1/PD-L1 antibodies develop more frequent and severe toxicities compared with monotherapy with these drugs.

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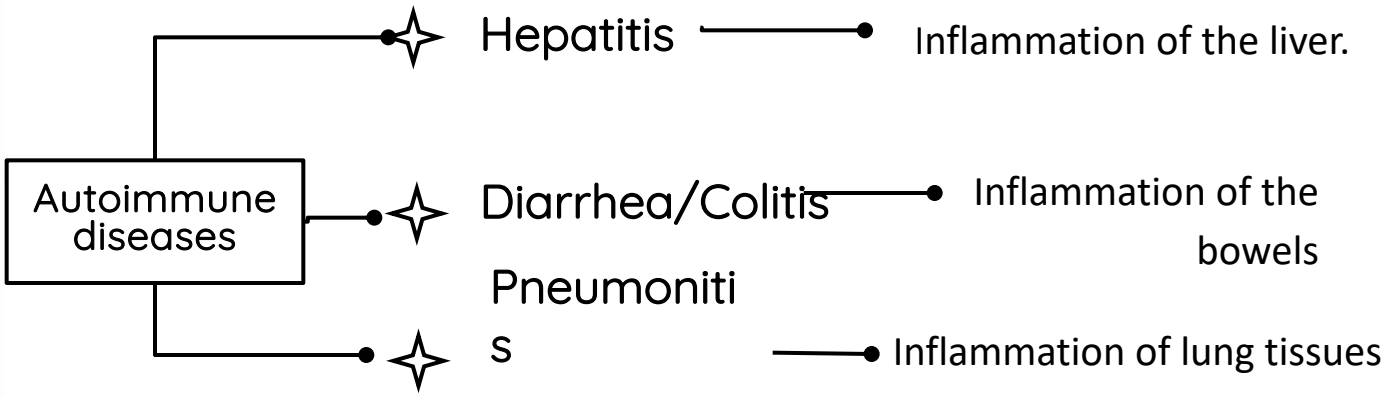
Autoimmune Complications

Autoimmune complications

The most common side effects associated with immunotherapy are inflammatory conditions that can affect different parts of the body.



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Autoimmune complications

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Autoimmune diseases

- **Hepatitis**
  - Hepatitis occurs in up to **1% to 7%** of patients during **monotherapy with ipilimumab** and **1% to 6%** of patients treated with **anti–PD-1/PD-L1 antibodies nivolumab or pembrolizumab.**
- **Diarrhea/Colitis**
  - In clinical trials of patients treated with **ipilimumab,** the incidence rates of diarrhea and colitis are **23% to 33% (grade 3/4, 3%–6%) and 8% to 12% (grade 3/4, 7%–9%).**
- **Pneumonitis**
  - The incidence of all-grade (3.8% vs. 2.3%), or **grade 3–4 pneumonitis (2.3% vs. 1.5%) in nivolumab plus ipilimumab group** was higher than that in the nivolumab monotherapy group

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Medications That Cause Autoimmune Complications

Immunotherapy Medications And Their AEs

TABLE 1. AEs of FDA-Approved Cancer Immunotherapies[1-6]

Agent	Target	Common AEs of any grade
Ipilimumab	CTLA-4	Fatigue, diarrhea, increased ALT, hyperglycemia
Pembrolizumab	PD-1	Fatigue, rash, hyperglycemia, hypertriglyceridemia
Nivolumab	PD-1	Fatigue, diarrhea, rash, increased ALT
Cemiplimab	PD-1	Fatigue, rash, diarrhea, musculoskeletal pain
Atezolizumab	PD-L1	Anemia, fatigue, decreased appetite, diarrhea
Avelumab	PD-L1	Fatigue, lymphopenia, anemia, increased AST

AEs, adverse effects; ALT, alanine transaminase; AST, aspartate aminotransferase.

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Steroids Used to Manage Immunotherapy Side Effects

Steroids used to manage Autoimmune side effects

Glucocorticoids are the mainstream therapy for irAEs.

Principles for the use of GCS recommended by NCCN guidelines

irAE	Grade	Type of hormone	Initial dose (mg/kg/day)
Dermatologic			
	G2	Prednisone	0.5–1
	G3-4	Prednisone/Methylprednisolone	0.5–1–2
Diarrhea/colitis			
	G2	Prednisone/Methylprednisolone	1
	G3-4	Methylprednisolone	2

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Wang, H., Zhou, J., Guo, X., Li, Y., Duan, L., Si, X., & Zhang, L. (2020). Use of glucocorticoids in the management of immunotherapy-related adverse effects. Thoracic cancer, 11(10), 3047–3052. https://doi.org/10.1111/1759-7714.13589

Steroids used to manage Autoimmune side effects

Glucocorticoids are the mainstream therapy for irAEs.

Principles for the use of GCS recommended by NCCN guidelines

Hepatic toxicity			
	G2	Prednisone	0.5–1
	G3	Prednisone/Methylprednisolone	1–2
	G4	Methylprednisolone	2
Pancreatitis			
	G2	Prednisone/Methylprednisolone	0.5–1
	G3 ~ 4	Prednisone/Methylprednisolone	1–2

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Wang, H., Zhou, J., Guo, X., Li, Y., Duan, L., Si, X., & Zhang, L. (2020). Use of glucocorticoids in the management of immunotherapy-related adverse effects. Thoracic cancer, 11(10), 3047–3052. https://doi.org/10.1111/1759-7714.13589

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Severe Side Effects of Steroids

- Increased Risk of Infections
- Low Level of Potassium in Blood
- Blood Clots
- Inflammation of Pancreas and Liver
- Muscle Wasting
- Cushing's Syndrome

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Alternative Drugs to Steroids to Treat Autoimmune Side Effects

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Cases

- **Case #1**
- 70 y/o
- Dx 2018 melanoma stage IIb (pT3bN0, Breslow 3.65mm, ClarkIV, with ulceration and negative SLN.
- Ten months later two new lesions in the back
- Refused adjuvant therapy
- One month later new relapse
- Molecular test negative for BRAF mutation
- Tx started with nivolumab 480mg every 4 weeks .
- After 6 cycles anti-programmed cell death 1, he had progression
- Nivolumab was discontinued
- Ipillimumab 3mg/Kg was started as 2nd line
- LFT's were normal prior to the start
- One week after the 4th dose was admitted with fever, weaknes for 2 days.
- Hematology WNL serum endocrine parameters showed moderate hypophysitis.
- At the time of admission serum transaminase and cholestatic enzymes were had grade 4 elevaton: AL=ST 783 IU, ALT 1029 IU/L, grade 2 GGT 147IU/L, grade 2 bilirubin 1.9mg/dl

https://doi.org/10.1136/jitc-2020-001322

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Case#1 (cont)

- All viral workup negative
- All autoimmune testing negative
- Due co-existence of immune –mediated hypophysitis, a strong suspicioun for an immunological origin hepatitis
- Treatment with methylprednisolone 1mg/Kg.
- Two days later liver biochemistry continued to worsen
- Steroid dose increased to 2mg/Kg
- To prevent opportunistic infection Trimethoprim-Sulfamethoxazole was added 400mg daily
- No biochemical response
- Mycophenolate mofetil (MMF) 1000mg IV bid started and
- Ursodeoxycholoic acid at a dose of 500mg bid.
- Due to thrombocytopenia MMF caused, dose was reduced to 500mg bid
- Multidisciplinary team co-managed –medical oncologist, hepatologist, internist.
- A third immunosuppressant agent added: tacrolimus 1.5mg bid to target levels of 8 and 10ng/ml
- Liver biopsy omitted due to not enough evidence to support and fear of risk of hemorrhage
- LFT showed remarkable improvement and steroid weaning was initiated.

https://doi.org/10.1136/jitc-2020-001322

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Cases (cont)

- Patient was discharged after 63 days in the hospital
- For grade ¾ toxicity ICPI's should be permanently discontinued.

Case #2

- 65 y/o male with Hx of stage III melanoma, resected from the right axilla and
- CT scan revealed metastatic disease with multiple pulmonary nodules, bx proven. BRAF wild type
- Hx included prostrate cancer early 18 months before, treated with surgery
- Started single agent pembrolizumab every 3 weeks.
- At 12 weeks CT scan revealed near-completed response
- Afer his 5th dose he noted diarrhea (did not report to team) and improved after 3 days
- Two weeks after the after the 5^{th} dose noted 8 episodes in 24 hours accompanied by cramping
- He finally called the team when his conditioned worsened and blood pressure dropped to 95/50, tachycardia and abdominal tenderness
- Rectal exam heme negative, bun 37mmol/L with creatinine 1.5.
- CT scan revewied stranding and thickening of descending and sigmoid colon without free air
- C difficile was negative

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Case #2 (cont)

- IV fluids started
- Methylprednisolone 125mg IV x 2
- Diarrhea decreased to 4 times a day in the next 24 hrs
- He continued with diarrhea 4 x in 24 hours
- Gastroenterologist performed a sigmoidoscopy, which showed diffuse ulceration and erythema.
- A dose of infliximab 5mg/Kg was ordered –there was delayed due insurance issues
- Discussion with hospital administration regarding NCCN guidelines recommendations, patient was able to receive
- He reported feeling better after 24 hrs
- Corticosteroids were continued at 120mg prednisone daily
- Discharged to home after 5 days in the hospital
- Afer 48hours without diarrhea the corticosteroids were tapered over 48 days by 10mg every 4 days
- Repeat CT at week 24 demonstrated a complete response with no evidence of disease and has been maintained for 2 years.

2018 asco educational book/asco.org/edbook

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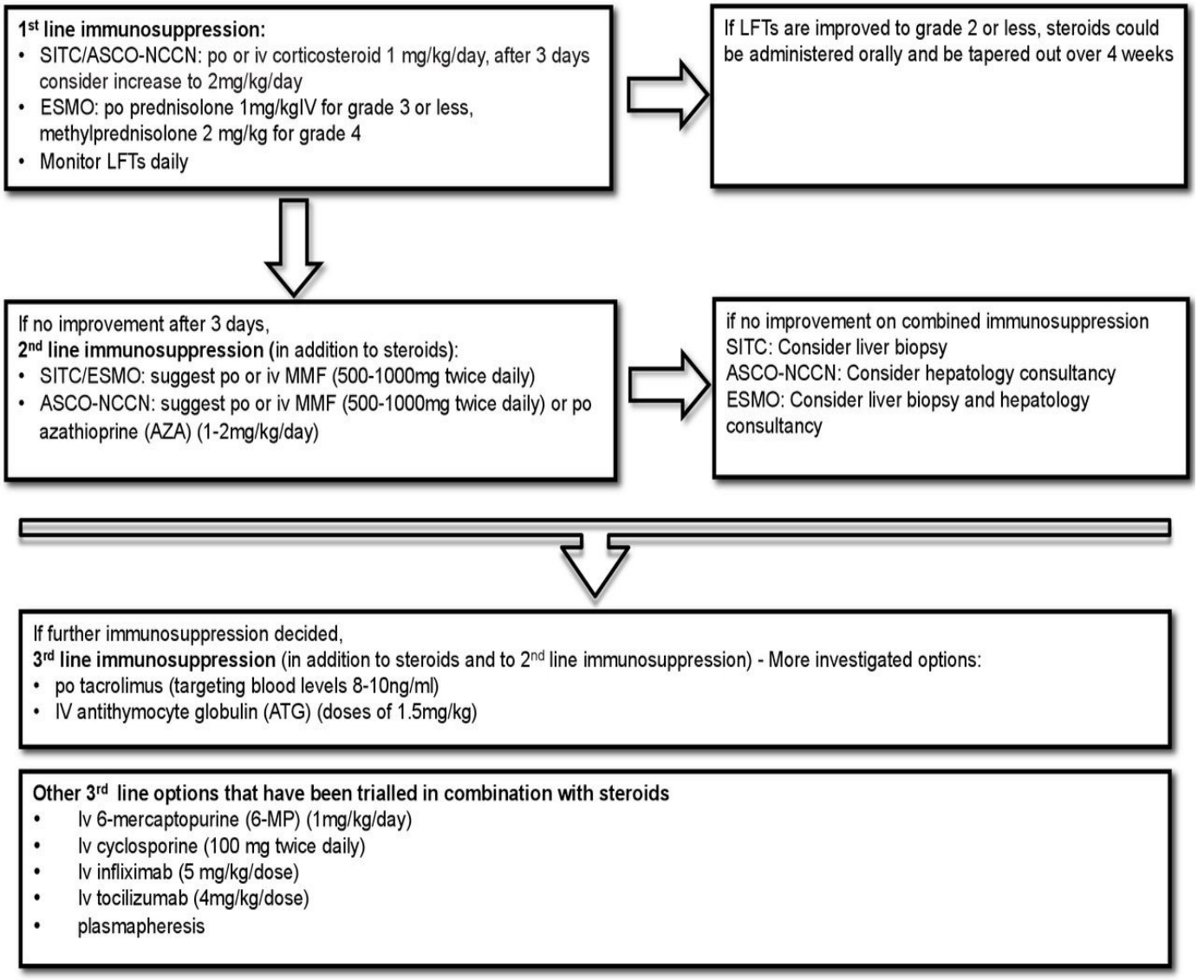
A suggested algorithm for the addition of further immunosuppressive options after steroid failure in ir-hepatitis and the differentiations between oncology societies.



Dimitrios C Ziogas et al. J Immunother Cancer 2020;8:e001322

Alternative drugs to Steroids for Managing Autoimmune Disease Symptoms

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- Drugs (continued)
  - Cyclosporin, 2mg /Kg/day to 5mg/Kg/day
  - Tacrolimus, 0.5mg/day to 3mg twice a day
  - Budesonide, 3mg three times/day combined with azathioprine

Czaja A. J. (2012). Autoimmune hepatitis: focusing on treatments other than steroids. Canadian journal of gastroenterology = Journal canadien de gastroenterologie, 26(9), 615–620. https://doi.org/10.1155/2012/512132

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Conclusion

- Steroids have been the first treatment to treat immunotherapy toxicities
- Early recognition of irAE's and a multidisciplinary approach is paramount
- High dose steroids work, however, there could be steroid induced side effects, which is detrimental to the homeostasis of the patient.
- Sometimes there is a need for additional armament to treat these irAE's and knowing the guidelines and recommendations is essential.
- Clearly more research is needed in regards to management of irAE's.

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Mahalo

Gracias

Thank
You!

Grazie

Obrigado

Merci

Bedankt

Danke