TB and Old and New Biologics

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DISEASE PREVENTION & CONTROL

E-consult request

“84 year old with hepatocellular cancer with likely pulmonary metastases, will be starting immunotherapy, has latent TB, no symptoms/signs of active TB. She has abnormal LFTS. Do you have recommendations for LTBI treatment?”

What are next steps?

Medical Record Dive

- 84 year old female recently arrived from El Salvador
- History of diabetes, hypertension, gout, cirrhosis and per patient, newly diagnosed with hepatocellular cancer in El Salvador
- Presented to the ED with complaint of cough and abdominal pain x 3 months
- Imaging showed intraventricular septal mass, bilateral large solid pulmonary nodules, mediastinal lymphadenopathy and a 9.6 x 4 cm liver mass extending into the portal vein and peritoneum consistent with stage IV metastatic liver cancer
- IGRA positive
- AST 147, ALT 125, alk phos 185, T bili 1.5
- Planned immunotherapy: **atezolizumab and bevcizumab**

Approach

- Consider whether there is concern for active pulmonary TB (this is a frequent clinical conundrum, and there is no one good answer)
- Is the patient at risk for TB reactivation?
- Look up the recommended immunotherapy-

    Atezolizumab – PDL1 inhibitor

    Bevcizumab – VEGF inhibitor

Are these immunosuppressing drugs comparable to traditional chemotherapy?

With regard to TB…

New Biologics (Immunologist-speak)

- The use of new targeted immunotherapies (or biologics) has radically transformed the available treatment options for many chronic diseases.
- These targeted immunotherapies work by blocking specific molecules that mediate certain immune responses or by depleting the cells that express them.
- Some can also increase the risk of progression to active TB disease by downregulating the immunologic functions that contain TB organisms.

https://www.sfcdcp.org/tb-control/tuberculosis-information-for-medical-providers/tb-ti-recommendations/

TNF Inhibitor Biologics

- Risk varies by drug class and mechanism of action.
- Tumor necrosis factor (TNF)-alpha inhibitors has been associated with high risk of progression of TB; the active TB infection has a greater likelihood of involving extra-pulmonary sites and of being disseminated at presentation.
- Risk has been reported to be greater with infliximab and adalimumab than with etanercept.
- Latent TB infection (LTBI) screening and treatment appears to significantly reduce the incidence of progression to active TB in these patients.

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Non -TNF Inhibitor Biologics

- There is growing evidence that other targeted immunotherapies (e.g., PD-1/PDL-1 inhibitors, CTLA-4 inhibitors, JAK kinase inhibitors, and IL-6 and IL-23 inhibitors to name a few) are also associated with increased risk of TB reactivation.
- These targeted immunotherapies should be treated similarly as for a TNF-inhibitor.
- SFDPH recommends that patients with a diagnosis of LTBI should be initiated on treatment for at least 1 month, if possible, prior to starting those targeted immunotherapies where a risk for TB progression has been identified.

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The Table lists targeted immunotherapies as of July 2023 where the manufacturer's package insert recommends TB testing. This list may not include all available targeted immunotherapies; check the manufacturer's package insert for details.

Targeted Immunotherapies and TB Risk, 2023

University of California San Francisco TB Targeted Immunotherapy Group (TB-TIG)

TB testing with interferon-gamma release assay or tuberculin skin test is recommended for the following targeted immunotherapies (per the manufacturers drug insert)

Drug Name	Mechanism/Target
Abatacept	Selective T-cell costimulation modulator, CTLA-4
Abrocitinib	Kinase inhibitor (JAK1)
Adalimumab	Anti-TNF-alpha mAb
Alemtuzumab	Anti-CD-52 mAb
Anakinra	IL-1 receptor antagonist
Baricitinib	Kinase inhibitor (JAK1/JAK2)
Brodalumab	Anti-IL-17 receptor mAb
Canakinumab	Anti-IL-1beta mAb
Certolizumab	Anti-TNF-alpha mAb
Deucravacitinib	Kinase inhibitor (TYK2)
Emapalumab	Anti-IFN-gamma mAb
Etanercept	Soluble TNF-alpha receptor
Golimumab	Anti TNF-alpha mAb
Guselkumab	Anti-IL-23 mAb
Inebilizumab	Anti-CD-19 mAb
Infliximab	Anti-TNF-alpha mAb
Ixekizumab	Anti-IL-17 mAb
Rilonacept	Soluble IL-1 receptor
Risankizumab	Anti-IL-23 mAb
Rituximab	Anti-CD-20 mAb
Ruxolitinib	Kinase inhibitor (JAK1/JAK2)
Sarilumab	Anti-IL-6 receptor mAb
Satralizumab	Anti-IL-6 receptor mAb
Secukinumab	Anti-IL-17 mAb
Spesolimab	Anti-IL-36 receptor mAb
Tildrakizumab	Anti-IL-23 mAb
Tocilizumab	Anti-IL-6 receptor mAb
Tofacitinib	Kinase inhibitor (JAK1/JAK2/JAK3)
Upadacinitib	Kinase inhibitor (JAK1)
Ustekinumab	Anti-IL-12 and IL-23 mAb
Vedolizumab	Anti-integrin (a4B7) mAb

Abbreviations: CTLA-4, Cytotoxic T-lymphocyte associated protein 4; mAb, monoclonal antibody; TNF, tumor-necrosis factor; IL, interleukin; IFN, interferon

Note: While the manufacturers' package insert does not mentioned risk of active TB for the PD-1 (programmed cell death-1) and PDL-1 (programmed cell death ligand-1) inhibitor class of drugs, use in animal models has demonstrated increased severity of TB infections and enhanced inflammatory response. TB infected PD-1 knockout mice exhibit markedly decreased survival compared to wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockage using a primate anti-PD-1 antibody was also shown to exacerbate TB infection in rhesus macaques. Pending further data, the SFDPH TB Clinic recommends TB testing prior to use of these classes of drugs (including atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, nivolumab/relatlimab and pembrolizumab).

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Important footnote

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Recommendation

Bevcizumab is a VEGF (vascular endothelial growth factor) inhibitor- probably no increased TB risk

Atezolizumab is a PDL-1 inhibitor- probable increased TB risk based on animal studies

Recommendation: Treat for latent TB with levofloxacin for 9 months

Final Thoughts

- The number of new biologics (targeted immunotherapies) is growing exponentially.
- None seem to convey the same high TB risk as TNF-inhibitors, but time will tell.
- While the FDA-reviewed package insert is a good start, some of the recommendations are based on theoretical risk, while others do not take into account animal studies or are based on older data.
- As further data emerges, recommendations may change.
- In the meanwhile, following the package insert may be the most appropriate and conservative approach.