Gloucestershire Hospitals NHS Foundation Trust

Guideline for Tuberculosis screening for Biologic and Immunomodulatory drugs for inflammatory conditions

Introduction

Biological and immunomodulatory medicines are used in the management of inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis and psoriasis. They modify the actions of the immune system which can drive inflammation and disease progression, but this can also affect pathways which protect against infections.

This guideline does not apply to patients receiving immunosuppressive drugs for organ transplantation

As the number of available agents with varying targets has increased significantly in recent years, there has been a focus on minimising the effect on the immune system. As a result, some of the drugs have an associated risk of reactivating tuberculosis (TB), some have a lower risk and for some the risk is unclear.

Guidance is required to provide clarity over which drugs and therefore patients require TB screening prior to initiation of biological therapy, and how we do this.

- **Patients who are prescribed a GREEN drug DO NOT require a TB screen**
- **Patients who are prescribed a RED or AMBER drug do require a TB screen**

Amber drugs are lower risk for reactivating TB so should be used in preference to Red drugs if the patient is thought to have a high risk of TB reactivation.

All parts of the TB screen are required for its completion:

- **A chest X ray to rule out abnormalities**
- **A T spot blood test***
- **A series of questions to the patient:**
  - Does the patient have any symptoms of TB? (cough >3 weeks/unexplained weight loss/fevers/night sweats)
  - Immunosuppressed already** AND Resident (>3 months) in a country with a high incidence of TB within the last 5 years?
  - Have they had contact with a known case of TB?
  - Have they previously had TB?

* If the patient has ever had a positive T spot test, then do not repeat the T spot in any circumstances as it will be inaccurate

**Immunosuppressed is defined as being prescribed the following medications:

Prednisolone >15mg/day >1 month, Methotrexate, Azathioprine, Leflunomide, Ciclosporin, Mycophenolate, Tacrolimus or with end stage renal failure i.e., dialysis or transplant

Patients who are immunosuppressed may have a false negative T spot

Written by: Dr Andrew White and Leela Terry (incorporating guidelines provided by Imperial Healthcare NHS Trust and University Hospitals Bristol NHS Foundation Trust)
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Tuberculosis screening additional notes

1. Latent tuberculosis infection (LTBI) testing and treatment should not delay the urgent treatment of serious disease, it is acceptable to proceed if the patient is believed to be low risk and has received a chest X ray**.**
2. If the responses are no to all questions/investigations are negative then no TB service referral is required but if there are any yes responses or positive investigations then the patient should be referred
3. Steroid prescribing does not require TB screening as routine, but there is an increased risk of TB reactivation, albeit less so than many of the other immunosuppressive and biological agents.
4. All patients receiving RED or AMBER drugs should be asked the screening questions routinely during clinical reviews to identify any possible changes and additionally where specified for other drugs within the table**.**
5. If the patient is being initiated on a GREEN drug but there is a high possibility that they will be switched to an AMBER/RED drug in the future, it is reasonable to undertake the full TB screen as it is likely to be more accurate. The patient will not necessarily need LTBI treatment at this point and it is important to discuss this with the patient.

Specific scenarios:

- **Patient being switched from GREEN to RED/AMBER drugs:**
  Refer to point 5 above, however regardless of whether the TB screen was undertaken at this stage or not, the patient should be asked the screening questions and a repeat chest X ray should be undertaken. If any significant new exposure is identified then a T spot should be repeated (only if previously negative) before initiating treatment.

- **Patient being switched from one RED/AMBER drug to another RED/AMBER drug:**
  The patient should be asked the screening questions and if any significant new exposure is identified, a repeat T-spot should be undertaken (only if previously negative). If the patient additionally has new respiratory symptoms, then a repeat chest X ray should also be undertaken prior to initiating treatment.

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Risk of TB reactivation for Biologic and Immunomodulatory Drugs

Therapeutic target	Specific drug examples	ESGICH Consensus Document: Is TB testing recommended?	Summary of Product Characteristics: Is TB testing recommended?	Comments
TNFα (monoclonal antibody)	Infliximab, adalimumab, golimumab, certolizumab pegol	Yes	Yes	Relatively high risk for reactivating TB
TNFα (soluble receptor)	Etanercept	Yes	Yes	Etanercept thought to be lowest risk of all anti-TNF
IL-4	Dupilumab	Not reviewed	No	
IL-5	Benralizumab, Mepolizumab	No	No	
IL-6	Tocilizumab, sarilumab	Yes	Yes	Rate of TB cases lower than background TB risk (in RA patients)
IL-12/23 common p40 subunit	Ustekinumab	Yes	Yes	No TB cases associated with ustekinumab (in PsA and AS patients)
IL-13	Tralokinumab, lebrikizumab	Not reviewed	No	
IL-17	Brodalumab, Bimekizumab, Ixekizumab, Secukinumab	Yes	Yes	Thought to be low risk but recommendation to screen. No cases seen in PsA and AS patients with secukinumab
IL-23	Guselkumab, risankizumab, tildrakizumab, mirikizumab	Not reviewed	Yes	
IgE	Omalizumab	No	No	
Complement factor E5	Eculizumab	No	No	
Janus kinases	Baricitinib, filgotinib, tofacitinib, upadacitinib, abrocitinib, ritlecitinib	Yes	Yes	
TYK 2	Deucravacitinib	Not reviewed	Yes	
CD20	Rituximab, ofatumumab, ocrelizumab	No	No	
CD28	Abatacept	Not reviewed	Yes	
CD52	Alemtuzumab	Yes	Yes	

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Integrin α4β1	Natalizumab	No	No	
Integrin α4β7	Vedolizumab	No	Yes	
Sphingosine 1-phosphate receptor	Fingolimod, siponimod fumaric acid, ponesimod, ozanimod, etrasimod	No	No	Theoretical risk but no cases seen in trials
Nucleoside analogue	Cladribine	Not reviewed	Yes	
Non specific	Dimethyl fumarate, diroximel fumarate	Not reviewed	No	
Mitochondrial enzyme dihydroorotate dehydrogenase	Leflunomide	Not reviewed	Yes	Only ask patient questions, do not proceed to T spot/CXR unless positive response to any question
	Teriflunomide	Not reviewed	No	
Non specific	Glatiramer acetate	Not reviewed	No	
PDE4	Apremilast	Not listed	No	
Inosine monophosphate dehydrogenase	Mycophenolate	Not listed	No	Consider asking patient screening questions at annual review
Non specific	Ciclosporin	Not listed	No	
Non specific	Interferon beta	Not listed	No	
Dihydrofolate reductase	Methotrexate	Not listed	No	Consider asking patients screening questions at annual review
Non-specific	Azathioprine, 6-mercaptopurine	Not listed	No	Doses below 3mg/kg/day are not considered especially immunosuppressive Consider asking patient questions at annual review

References

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