Appendix

Expert Views on Screening for Tuberculosis Infection in Patients Commencing Treatment with a Biologic Agent

Table A1: Guidelines regarding LTBI screening and treatment for patients undergoing treatment with biologic agents

Medical Society	Screening before biologic initiation?	Type of screening	Guideline specific for biologic class?	How soon after LTBI treatment can they start biologics?	What type of LTBI treatment	Repeated LTBI testing + Routine Monitoring	Process of guideline development	Quality of sources
Arthritis Australia	Yes[1]	Not Available	Broad/All[1]	Not Available	Not Available	Not Available	Not Available	Not Available
Australian Rheumatology Association	Yes[2]	IGRA + CXR within last 3 months + History and risk factors[2].	TNF-α inhibitors[2]	Concurrently 1-2 months after beginning prophylaxis[2].	- Isoniazid + pyridoxine 6-9 months - Rifampicin 4 months[2]	Not Available	Not Available	Not Available
Australasian College of Dermatologists	Yes[3]	CXR + Blood tests (not specific for TB) [3].	Broad/All[3]	Not Available	Not Available	Not Available	Not Available	Not Available
Gastroenterological Society of Australia	Yes[4]	CXR + History and risk factors[4].	Broad/All[4]	Not Available	Not Available	Not Available	Not Available	Not Available

Australian Council on Healthcare Standards	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available
Australian General Practice Group	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available
National Tuberculosis Advisory Committee	Yes[5,6]	IGRA/TST. May be combined if high TB risk. + CXR, sputum culture + TB exposure history[6].	TNF-α Inhibitors[5,6]	Not Available	- Isoniazid 6-9 months - Rifampicin 4 months - Rifampicin + isoniazid 3 months[5]	Not Available	No systematic review done, but reference is made to selected articles[5]. Informed by meta-analyses and trials, but no systematic search was performed[6].	No reference is made to the strength/quality of literature informing recommendations[5]. Quality of evidence informing guidelines is not graded[6].
Lung Foundation Australia	Required in TNF-α inhibitor use, but not specified before treatment initiation[7].	TST preferred in most groups. CXR if positive IGRA/TST[7].	Not available	Not available	Not available	Not Available	Not Available	Not Available

Council of Australian Therapeutic Advisory Goods	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available
International League of Associations for Rheumatology	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available
American College of Rheumatology (ACR)	Yes – within the preceding 12 months[8].	TST /IGRA[9] Screening recommended regardless of LTBI risk factor presence[10]. CXR if positive TST/IGRA. Sputum sample if positive CXR[10].	TNF-α inhibitors[9] Abatacept should not be combined with TNF-α inhibitors[11] Broad/All[10]	After 1 month of LTBI treatment. After completion of active TB treatment[10]	Not Available	Annual LTBI screening if TB risk factors present or ongoing TB exposure[10]. Immunosuppressed RA patients with risk factors for LTBI and negative initial screening tests may consider repeat LTBI screening 1–3 weeks after[10].	Recommendations developed by 2 expert panels and informed by evidence from systematic literature reviews, including data from RCTs, prospective and retrospective cohort studies, and clinical trials. Guidelines were then peer-reviewed by over 30 members from the ACR[10]. No evidence cited for 3 sources[8,9,11].	Sources were all evaluated for strength and relevancy. TB recommendations were predominantly classified as level C, meaning they were mostly formed by expert opinion, case studies or standards of care[10].
European Alliance of Associations for	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available

Rheumatology (EULAR)								
COVID-19 International Rheumatology Alliance	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available	Not Available
British Society for Rheumatology	Yes[12]	TST and/or IGRA + CXR + History/risk factors Abnormal CXR/TB history should be referred to specialist. TST not helpful in patients on immunosuppressive therapy with normal CXR. Either positive TST or IGRA in immunocompromised	Broad/All[12] Consider etanercept over TNF-α inhibitor monoclonal antibodies for high risk patients[12]	At least 1 month of LTBI treatment[12] For active TB, after completing at least 3 months of treatment with evidence of culture negativity[12].	- Isoniazid 6 months - Rifampicin + isoniazid 3 months[12]	patients should be monitored every 3 months and up to 6 months after stopping treatment – repeat screening tests not explicitly explored[12].	Recommendations developed by expert panel based on evidence from a literature search including 289 articles[12].	GRADE method used to evaluate the quality of evidence. Recommendations were also individually evaluated based on strength of evidence. Quality of evidence was ranked moderate to very low for all TB-related recommendations[12].

		patients are considered for TB treatment[12].						
World Health Organisation	Yes[13]	TST or IGRA[13]	TNF-α inhibitors[13]	Not Available	Shorter treatments such as 1- or 3-months isoniazid + pyridoxine[13].	Not Available	Recent evidence was reviewed by the Guideline Development Group.	Certainty of evidence are low to very low.
British Thoracic Society	Yes[14]	History/risk factors + physical examination + CXR within last 3 months. TST if no immunosuppression history. Abnormal CXR/TB history referred to specialist[14].	TNF-α Inhibitors[14]	Complete at least 2 months LTBI treatment[14].	Not Available	Patients with abnormal CXR/ TB history receive repeat CXR 3 months after initial[14].	Systematic search of the literature and clinical expertise of guideline developers. Despite being evidence-based, they are outdated (2005) and only relevant to TNF-α inhibitor drugs[14].	Strength of literature was evaluated using a revised SIGN grading system and found to be mostly low for methodology[14].
British Association of Dermatologists	Yes[15,16]	IGRA alone or with TST + TB risk factors + CXR.	TNF-α Inhibitors IL-12/23 Inhibitors IL-17 Inhibitors IL-23 Inhibitors[15] All biologics[16].	Complete 2 months LTBI treatment[15,16].	- Isoniazid + pyridoxine + rifampicin 3 months - Isoniazid + pyridoxine 6 months[15].	Assessment and investigation including repeat IGRA on symptoms/signs suggestive of TB,	Not systematically reviewed[15]. Developed by a multi-disciplinary group based on a systematic literature search. Each included	Strength of recommendations were overall weak, and many were consensus-based[15].

		Assess for active TB and/or management of latent TB in consultation with TB specialist[15,16].				new TB exposure prolonged residence in a high incidence setting[15,16].	study was critically evaluated, and overall quality of evidence for recommendations was assessed using the GRADE method[16].	Overall, recommendations were rated to be strong[16].
National Institute for Health and Care Excellence (NICE) (UK)	Not Available	IGRA alone or with TST for immunocompromised[17] (not specific for biologic drugs).	Guidelines are not specific for use in patients on biologic drugs.	Not Available	- Isoniazid + pyridoxine + rifampicin 3 months - Isoniazid + pyridoxine 6 months[17]	Not Available	Developed by experts based on evidence from prospective and retrospective cohort studies, case-control studies, and cross-sectional studies[17].	Evidence reviewed is not specific for screening and treatment in patients initiating biologic treatment and is therefore of limited value[17].
National Psoriasis Foundation & American Academy of Dermatology	Yes[18]	TST or IGRA prior to IL-17,23 inhibitors. TST or IGRA for TNF-α, IL-12/23 inhibitors[18]. Referral for CXR with	TNF-α inhibitors IL-12/23 inhibitors IL-17 inhibitors IL-23 inhibitors[18]	Not Available	Not Available	Yearly re-testing in high-risk patients on all biologics, screening and annual CXR done at discretion of dermatologist in lower risk patients[18].	Developed by multi-disciplinary expert group and based on a literature review of 354 articles, the quality of each was evaluated using a 3-point scale.	Evidence from articles informing TB-specific guidelines were referenced but not graded or evaluated individually for strength or quality[18]. Hence the strength of recommendations is unknown.

		positive TB test[18].						
Spanish Society of Pneumology and Thoracic Surgery (SEPAR)[19]	Yes[19]	- Detailed history - CXR and if doubt include CT Chest -Simultaneous IGRA and TST. A positive result in any of these tests is considered indicative of LTBI (III)[19].	All biologics[19]. TNF-α has highest risk especially infliximab and adalimumab[19].	4 weeks[19]	Isoniazid for 9 months. In exceptional cases only, treatment with isoniazid + rifampicin for 3 months. In the event of isoniazid-induced hepatotoxicity, rifampicin for 4 months is recommended[19].	Only when symptomatic or after possible exposure after travel to highly endemic areas (III)[19].	Developed by a team of experts specialising in treatment with biologics using evidence from literature. All recommendations are graded using the classification of the American Society of Infectious Diseases.	All recommendations included in this table were based on expert opinion (grade III) or on weaker quality evidence (grade II).

European Society of Clinical Microbiology and Infectious Disease (ESCMID) [20]	Yes[20]	Dual TST and IGRA Risk factor assessment and active TB exclusion[20].	TNF-α inhibitors[20]	Not Available	Not Available	Unclear; routine annual re-screening should be considered[20].	Multidisciplinary team reviewed the available evidence from a large literature search.	Sources included meta-analyses of RCTs, post-marketing registries and retrospective cohort studies. Sources and strength of recommendations was not assessed.
European Society of Clinical Microbiology and Infectious Disease (ESCMID) [21]	No: IL-5[21] Yes: IL-17, IL-12/23, IL-6, IL-1[21]	Not Available	IL-1 inhibitors IL-5 inhibitors IL-6 inhibitors IL-12/23 inhibitors IL-17 inhibitors[21]	Not Available	Not Available	Not Available	Multidisciplinary team reviewed the available evidence from a large literature search.	Sources included meta-analyses of RCTs, post-marketing registries and retrospective cohort studies. Sources and strength of recommendations was not assessed.
Rituximab Consensus Experts Committee[22]	No – not necessary for patients with rheumatoid arthritis[22].	N/A	Rituximab[22]	N/A	N/A	N/A	A systematic literature review was performed to collect data for discussion by an expert committee.	Evidence viewed was only for patients with rheumatoid arthritis. Outdated (2011). Strength of recommendations not assessed.

Drugs and Bulletin Board of Navarre, Spain[23]	Yes[23]	TST with IGRA if negative TST result, and CXR to exclude active TB[23].	TNF-α inhibitors IL-12/23 inhibitors IL-17 inhibitors IL-6 inhibitors abatacept[23].	1-2 months after LTBI treatment is completed[23].	Start isoniazid 300 mg/day or 900 mg twice weekly for 6 (65% effectiveness) to 12 months (75% effectiveness[23].	Repeat yearly for patients with risk factors on TNF-α inhibitors[23].	Literature search conducted. Recommendations based on evidence for TNF-α inhibitors are extended to the other biologic classes despite lack of evidence[23].	Data from clinical trials, systematic reviews, and national registries. Quality of sources and recommendations not individually evaluated.
Centers for Disease Control and Prevention (USA) [24]	Yes	History/risk factors. TST[24].	TNF-α inhibitors[24]	Until completion of LTBI treatment[24].	9 months isoniazid[24]	Not Available	Based mostly on case reports of TB reactivation.	Outdated (2004).
Clinical Standards for the diagnosis, treatment and prevention of TB Infection[25]	Yes	TST or IGRA (not specific for patient undergoing biologics)	All biologics	N/A	WHO recommende3d regimens, not differentiating for patients undergoing biologics	Not Available	Delphi process	Updated literature search

Brazilian Thoracic Association[26]	Yes	TST with induration of 5mm or more considered positive.	Guidelines not specific for any biologic, but specifically includes patients undertaking treatment with TNF-α inhibitors as immunocompromised individuals[26].	At least one month[26].	6 months isoniazid. Combination of isoniazid and rifampicin for 3 months or 2-4 months rifampicin alone[26].	TST should be periodically performed in patients with initial negative TST result[26].	Literature search conducted, and level of evidence of each source analysed by topic editors with Oxford Centre for Evidence-based Medicine criteria[26].	Outdated (2009). Not specific for TNF-α inhibitors.

Abbreviations: CXR= Chest X-ray, IGRA= Interferon Gamma Release Assay, IL= Interleukin, TBI= Tuberculosis Infection, N/A= Not Applicable, RCT= Randomised Control Trial, TB= Tuberculosis, TNF-α= Tumour Necrosis Factor Alpha, TST= Tuberculin Skin Test

Table A2: Survey participants' preferred TBI screening practices

	TST only	IGRA only	IGRA for BCG vaccine, TST for others	TST/IGRA without preference	TST and IGRA sequentially if the first is negative	Total responses	Blank responses	Grand total
Number of participants	6/147 (4%)	53/147 (36%)	15/147 (10%)	24/147 (16%)	49/147 (33%)	147	16	163

Abbreviations: BCG= Bacillus Calmette-Guérin, IGRA= Interferon Gamma Release Assay, LTBI= Latent Tuberculosis Infection, TST= Tuberculin Skin Test

Table A3: Survey participants' opinions on when TBI Screening should be repeated

LTBI Screening should be repeated:	Number of participants
On exposure to an infectious TB patient	43/146
Travel to high TB incidence country	5/146
At regular intervals (e.g. annually) even in the absence of new TB exposure risks	23/146
In vulnerable populations e.g. HIV, high TB incidence background	1/146
Different approach based on baseline results	2/146
Uncertain/ Lack of evidence only	0
On new exposure + travel to high TB incidence country	37/146
On new exposure + travel to high TB incidence country + at regular intervals	17/146
On new exposure + travel to high TB incidence country + at regular intervals + depends on baseline results	1/146
On new exposure + travel to high TB incidence country + in vulnerable populations	3/146
On new exposure + at regular intervals	11/146
On new exposure + different approach based on baseline results	1
On new exposure + Uncertain/ Lack of evidence	1
Never	1
Total Responses	146
Blank Responses	17

Abbreviations: HIV= Human Immunodeficiency Virus, TBI= Tuberculosis Infection, TB= Tuberculosis

Table A4: Survey respondents' suggestions on duration of tuberculosis preventive therapy (TPT) before initiation of biologic treatment

TB incidence in respondents' country of practice	1 month	2 months	3 months	Completed treatment	other	Total responses	Blank responses	Grand total
Low	71/102 (70%)	5/102 (5%)	9/102 (9%)	9/102 (9%)	8/102 (8%)	102	12 (12/144=8%)	114
Intermediate to high	22/ (56%)	2/ (5%)	4/ (10%)	7/ (18%)	4/39 (10%)	39	9 (9/48=19%)	48
Not provided	0	0	0	1/1 (100%)	0	1	0	1
Total	93/142 (65%)	7/142 (5%)	13/142 (9%)	17/142 (12%)	12/142 (8%)	142	21	163

Abbreviations: TB= Tuberculosis

Table A5: Guideline recommendations for or against tuberculosis infection (TBI) screening for different biologic agents and survey respondents recommending for and against screening

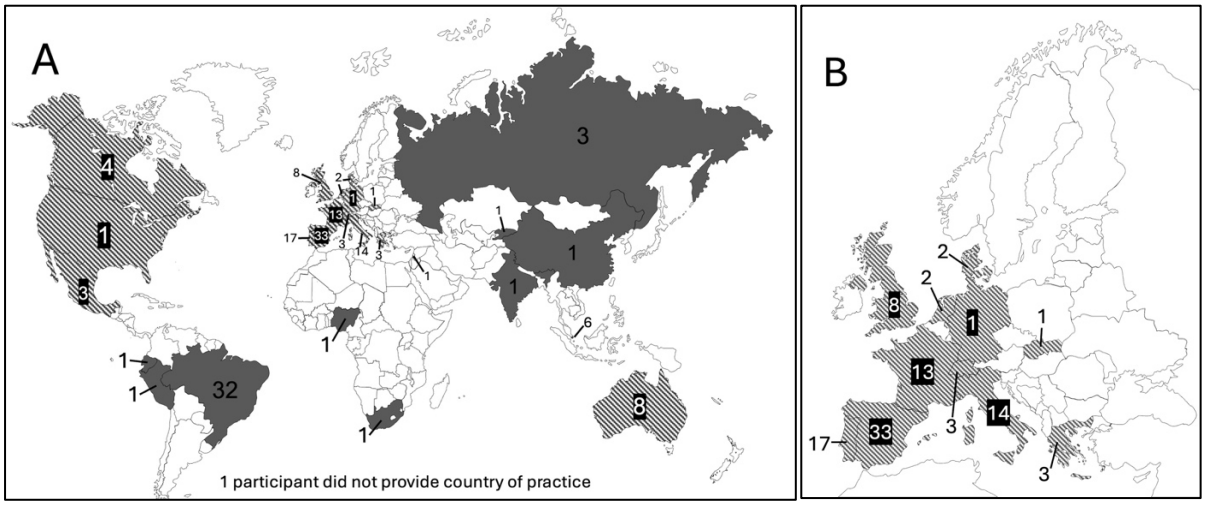
Biologic Agent	Guidelines recommending screening	Guidelines not recommending screening	Percentage of survey respondents recommending any screening (IGRA/TST/CXR)	Percentage of survey respondents recommending against screening
Infliximab	(WHO) [13] (SEPAR) [19] ESCMID[21]		97% (152/157)	0
Adalimumab	(WHO) [13] (SEPAR) [19] ESCMID		98% (147/150)	0
Etanercept	(WHO) (SEPAR) [19] ESCMID		98% (145/148)	0
Certolizumab pegol	(WHO) [13] (SEPAR) ESCMID		90% (129/144)	0
Golimumab	(WHO) [13] (SEPAR) ESCMID		91% (130/143)	0
Abatacept	(SEPAR) Drug and Bulletin Board of Navarre, Spain[23]		73% (102/140)	3% (4/140)
Rituximab	(SEPAR)	Rituximab Consensus Experts Committee[22] NHS Gloucestershire Hospitals guideline[27]	64% (91/142)	15% (21/142)

Sarilumab	NHS Gloucestershire Hospitals guideline, (SEPAR) Drug and Bulletin Board of Navarre, Spain[23]		54% (76/141)	7% (10/141)
Tocilizumab	NHS Gloucestershire Hospitals guideline, (SEPAR) Drug and Bulletin Board of Navarre, Spain[23]		60% (85/141)	11% (16/141)
Mepolizumab	(SEPAR)	ESCMID[21], NHS Gloucestershire Hospitals guideline	33% (46/138)	31% (43/138)
Benralizumab	(SEPAR)	NHS Gloucestershire Hospitals guideline	32% (44/138)	31% (43/138)
Ustekinumab	(SEPAR) ESCMID, NHS Gloucestershire Hospitals guideline, Drug and Bulletin Board of Navarre, Spain[23]		50% (70/140)	11% (15/140)
Secukinumab	(SEPAR) NHS Gloucestershire Hospitals guideline, Drug and Bulletin Board of Navarre, Spain[23]		46% (63/137)	10% (13/137)

SEPAR and WHO guidelines do not specifically name all biologics and extend recommendations to all biologics (SEPAR) or to all TNF-alpha inhibitors (WHO).

Abbreviations: CXR= Chest X-ray, ESCMID = European Society of Clinical Microbiology and Infectious Diseases, NHS= National Health Service (United Kingdom), SEPAR = Spanish Society of Pulmonology and Thoracic Surgery, WHO = World Health Organisation

Figure A1: Survey participants' country of practice



A: Survey participants' country of practice grouped by tuberculosis (TB) incidence rate.
B: Survey participants' country of practice grouped by TB incidence rate in Europe
Low TB incidence countries (<40 cases per 100,000 per year) are patterned.

Intermediate-to-high TB incidence countries (>40 cases per 100,000 per year) are coloured in gray.
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References

1. Arthritis Australia. Things to consider when taking a biologic. https://arthritisnsw.org.au/wp-content/uploads/2018/08/ThingsToConsiderBiologic-Infosheet.pdf (Arthritis Australia, 2017).
2. Australian Rheumatology Association. Screening for Latent Tuberculosis Infection (LTBI) and its management in Inflammatory arthritis patients. https://rheumatology.org.au/Portals/2/Documents/Public/Professionals/SCREENINGFORLATENTTUBERCULOSISINFECTION_Jan18.pdf?ver=2021-06-28-141621-710 (Australian Rheumatology Association, 2018).
3. Brown, P. Biological Treatments Used in Dermatology. https://www.dermcoll.edu.au/wp-content/uploads/2021/05/Biologics-A-Z-of-Skin.pdf (Australasian College of Dermatologists, 2020).
4. Alex, G. et al. Inflammatory Bowel Disease Updated 2018. https://www.gesa.org.au/public/13/files/Education%20%26%20Resources/Clinical%20Practice%20Resources/IBD/2018_IBD_Clinical_Update_May_update.pdf (Gastroenterological Society of Australia, 2018).
5. Stock, D. National Position Statement for the Management of Latent Tuberculosis Infection. https://www1.health.gov.au/internet/main/publishing.nsf/Content/C093439127C9A6CBCA258209000B4ABF/$File/CDI4103-d.pdf (National Tuberculosis Advisory Committee, 2017).
6. Bastian, I. & Coulter, C. Position statement on interferon-γ release assays for the detection of latent tuberculosis infection. https://www1.health.gov.au/internet/main/publishing.nsf/Content/4A5C7E747C705B0ACA25823C00068704/$File/cdi4104-c.pdf (National Tuberculosis Advisory Committee, 2017).
7. State Government of Victoria. Management, control and prevention of tuberculosis | Guidelines for health care providers. https://content.health.vic.gov.au/sites/default/files/migrated/files/collections/policies-and-guidelines/t/tb-guidelines-2015.pdf (State Government Victoria, 2015).
8. American College of Rheumatology. 2022 ACR Rise Registry Recommended Quality Measures List. https://www.rheumatology.org/Portals/0/Files/RISE-Recommended-Quality-Measures.pdf?ver=hHPV-WztsSGE-gvRb-0gMg%3D%3D (American College of Rheumatology, 2022).
9. American College of Rheumatology. Patient Fact Sheet | TNF Inhibitors. https://www.rheumatology.org/Portals/0/Files/TNF-Inhibitors-Fact-Sheet.pdf?ver=Lcm4TJsQpJzPXWqLZn7DCg%3D%3D (American College of Rheumatology, 2019).
10. Singh, J.A.*, et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* **64**, 625-639 (2012).
11. American College of Rheumatology. Patient Fact Sheet | Abatacept (Orencia). https://www.rheumatology.org/Portals/0/Files/Abatacept-Orencia-Fact-Sheet.pdf?ver=K7OI2CAfw6uRr748Bhj95Q%3D%3D (American College of Rheumatology, 2019).

12. Holroyd, C.R.*, et al.* The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis—Executive summary. *Rheumatology* **58**, 220-226 (2019).
13. World Health Organisation. WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. (2020).
14. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-α treatment. *Thorax* **60**, 800 (2005).
15. Smith, C.H.*, et al.* British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. *British Journal of Dermatology* **183**, 628-637 (2020).
16. British Association of Dermatologists. Guidelines for biologic therapy for psoriasis. https://www.bad.org.uk/shared/get-file.ashx?id=5835&itemtype=document (British Association of Dermatologists, 2017).
17. Overview | Tuberculosis | Guideline | NICE. https://www.nice.org.uk/guidance/ng33 (accessed Mar 2021).
18. Menter, A.*, et al.* Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol* **80**, 1029-1072 (2019).
19. Mir Viladrich, I.*, et al.* Consensus Document on Prevention and Treatment of Tuberculosis in Patients for Biological Treatment. *Arch Bronconeumol* **52**, 36-45 (2016).
20. Baddley, J.W.*, et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). *Clinical Microbiology and Infection* **24**, S10-S20 (2018).
21. Winthrop, K.L.*, et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clinical Microbiology and Infection* **24**, S21-S40 (2018).
22. Buch, M.H.*, et al.* Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* **70**, 909 (2011).
23. Rodriguez, I.I. & Zamarbide, O.G. Risk of Infection Associated with Biological Agents Used for Autoimmune Inflammatory Diseases. *Drug and Therapeutics Bulletin of Navarre, Spain* **28**(2020).
24. Centers for Disease Control and Prevention. Tuberculosis Associated with Blocking Agents Against Tumor Necrosis Factor-Alpha. (2004).
25. Migliori, G.B.*, et al.* Clinical standards for the diagnosis, treatment and prevention of TB infection. *Int J Tuberc Lung Dis* **26**, 190-205 (2022).
26. Conde, M.B.*, et al.* III Brazilian Thoracic Association Guidelines on tuberculosis. *J Bras Pneumol* **35**, 1018-1048 (2009).
27. Andrew White & Terry, L. Guideline for Tuberculosis screening for Biologic and Immunomodulatory drugs for inflammatory conditions. (2022).