Joint Statement (DZK, DGRh, DDG) on the Tuberculosis Risk with Treatment Using Novel Non-TNF-Alpha Biologicals

Gemeinsame Stellungnahme des Deutschen Zentralkomitees zur Bekämpfung der Tuberkulose (DZK), der Deutschen Gesellschaft für Rheumatologie (DGRh) und der Deutschen Dermatologischen Gesellschaft (DDG) zum Tuberkuloserisiko unter Therapie mit neuen Biologika (Non-TNF-alpha-Inhibitoren)

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ABSTRACT

Background While the risk of tuberculosis (TB) reactivation is adequately documented in relation to TNF-alpha inhibitors (TNFi), the question of what the tuberculosis risk is for newer, non-TNF biologics (non-TNFi) has not been thoroughly addressed.

Methods We conducted a systematic review of randomized phase 2 and phase 3 studies, and long-term extensions of same, published through March 2019. Of interest was information pertaining to screening and treating of latent tuberculosis (LTBI) in association with the use of 12 particular non-TNFi. Only rituximab was excluded. We searched MEDLINE and the ClinicalTrial.gov database for any and all candidate studies meeting these criteria.

Results 677 citations were retrieved; 127 studies comprising a total of 34,293 patients who received non-TNFi were eligible for evaluation. Only 80 out of the 127 studies, or 63 %, captured active TB (or at least opportunistic diseases) as potential outcomes and 25 TB cases were reported. More than two thirds of publications (86/127, 68 %) mentioned LTBI screening prior to inclusion of study participants in the respective trial, whereas in only 4 studies LTBI screening was explicitly considered redundant. In 21 studies, patients with LTBI were generally excluded from the trials and in 42

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out of the 127 trials, or 33\%, latently infected patients were reported to receive preventive therapy (PT) at least 3 weeks prior to non-TNF\(\alpha\) treatment.

**Conclusions** The lack of information in many non-TNF\(\alpha\) studies on the number of patients with LTBI who were either excluded prior to participating or had been offered PT hampers assessment of the actual TB risk when applying the novel biologics. Therefore, in case of insufficient information about drugs or drug classes, the existing recommendations of the German Central Committee against Tuberculosis should be applied in the same way as is done prior to administering TNFi. Well designed, long-term “real world” register studies on TB progression risk in relation to individual substances for IGRA-positive cases without prior or concomitant PT may help to reduce selection bias and to achieve valid conclusions in the future.

**ZUSAMMENFASSUNG**

**Hintergrund** Während das Risiko einer Reaktivierung der Tuberkulose (TB) durch TNF-alpha-Inhibitoren (TNFi) hinreichend dokumentiert ist, kann das Tuberkulose-Risiko beim Einsatz neuerer Nicht-TNF\(\alpha\)-Biologika bislang nur unzureichend eingeschätzt werden.

**Methoden** Wir führten ein systematisches Review zu 12 Nicht-TNF\(\alpha\)-Biologika durch und bezogen alle randomisierten Phase-2- und Phase-3-Originalstudien sowie deren Anschlussstudien ein, die bis März 2019 veröffentlicht wurden. Nur Rituximab wurde ausgeschlossen. Im Mittelpunkt des Interesses standen Informationen zum Screening auf und zur Behandlung von latenter Tuberkulose (LTBI). Durchsucht wurden die MEDLINE-Datenbank und das ClinicalTrial.gov-Register.

**Ergebnisse** 677 Publikationen wurden ermittelt, von denen 127 Studien mit insgesamt 34\,293 Patienten, die Nicht-TNF\(\alpha\)-Biologika erhalten hatten, evaluiert werden konnten. Nur in 80 der 127 Studien (63\%) war eine Tuberkulose (oder zumindest opportunistische Krankheiten) als potenzielle Nebenwirkung überhaupt erfasst worden; insgesamt wurden 25 TB-Fälle gemeldet. Mehr als 94 der Veröffentlichungen (86\% (127, 68\%) erwähnten ein LTBI-Screening vor Einbeziehung der Probanden in die jeweilige Studie, während ein LTBI-Screening in nur 4 Studien ausdrücklich als redundant angesehen wurde. In 21 Studien wurden Patienten mit LTBI grundsätzlich von der Studienteilnahme ausgeschlossen, und in 42 der 127 Studien (33\%) wurde berichtet, dass latent infizierte Patienten mindestens 3 Wochen vor der Nicht-TNF\(\alpha\)-Behandlung eine präventive Therapie erhalten hatten.


**Introduction**

An increased risk of TB reactivation in patients once infected with *M. tuberculosis* who receive inhibitors against TNF alpha (TNFi) has been adequately evaluated by several meta-analyses [1–3] and is addressed by the current recommendations of the German Central Committee against Tuberculosis [4]. Synthetic targeted or biological non-TNF\(\alpha\) disease modifying antirheumatic drugs (tsDMARD, bDMARD) including JAK-Inhibitors (JAKi) have further advanced the treatment of immune-mediated diseases such as rheumatoid arthritis (RA), axial spondyloarthritis, chronic inflammatory bowel diseases, psoriatic arthritis and psoriasis [5]. However, the association between non-TNF\(\alpha\) and an increased risk of TB remains uncertain. The best strategy for assessing the reactivation risk of patients due to the biologic’s immune suppressive activity is to compare patients with documented LTBI who had been administered the relevant drug (verum) on the one hand and patients not receiving the biologic on the other (placebo). Thus, with the aim of further investigating this issue, we performed an systematic in-depth review on the risk of TB between treatment (with non-TNF\(\alpha\)) and control groups only in randomised placebo-controlled phase 2 or phase 3 studies (with patients suffering from a defined target disease) or in long-term observations for the 12 tsDMARDs and bDMARDs approved for clinical practice in Germany at the onset of the observation period of our review: Abatacept, Anakinra, Apremilast, Baricitinib, Belimumab, Canakinumab, Ixekizumab, Secukinumab, Tocilizumab, Tofacitinib, Ustekinumab and Vedolizumab. Rituximab, a monoclonal antibody that selectively targets CD20-positive B cells for whom, according to an updated consensus statement [6], there is no evidence indicating the necessity to screen patients systematically for TB before using it, was not investigated. The compounds’ mechanisms of action can be seen in Table 1 together with their currently approved indications and forms of administration.

**Methods**

**Study selection**

We performed a MEDLINE search without limitations on publication years through 30 March 2019 for all published RCTs reporting TB risk. All study registrations for biologics in the...
database “ClinicalTrials.gov” were also examined, with these publications also being included in the pool of analyzed studies in addition to the literature search.

Search strategy
To ensure a maximum of sensitivity in assessing studies for therapeutic interventions using non-TNFi, the following search terms in MEDLINE were used:

- a) substance name AND tuberculosis
- b) substance name AND phase AND safety AND adverse events.

Three independent reviewers performed searches and selected articles meeting the inclusion criteria and one reviewer double-checked these data.

### Table 1 Summary of reviewed biologics in alphabetic order.

<table>
<thead>
<tr>
<th>Drug (trademark)</th>
<th>Mechanism of action</th>
<th>Currently approved indications (by 12/2019)</th>
<th>Form of administration</th>
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| Abatacept (Orencia) | Fusion protein, inhibition of CD 80 and CD 86 mediated T-cell response | - Rheumatoid arthritis  
- Psoriatic arthritis  
- Polyarticular juvenile idiopathic arthritis | Intravenous infusion 4 weekly or subcutaneous injection weekly |
| Anakinra (Kineret) | IL-1R Antibody, inhibition of Interleukin-1α and Interleukin-1β | - Rheumatoid arthritis  
- Still’s disease (juvenile and adult onset)  
- Cryopyrin-associated periodic syndromes (CAPS) | Subcutaneous injection, daily |
| Apremilast (Otezla) | Phosphodiesterase 4 (PDE4) inhibitor | - Plaque Psoriasis  
- Psoriatic arthritis | Orally, daily |
| Baricitinib (Olumiant) | Janus kinase inhibitor | - Rheumatoid arthritis | Orally, daily |
| Belimumab (Benlysta) | Antibody, inhibition of B-cell-activating factor (BAFF)/B-Lymphocyte Stimulator (BLyS) | - Systemic lupus erythematosus (SLE) | Intravenous infusion 4 weekly or subcutaneous injection weekly |
| Canakinumab (Ilaris) | Antibody, inhibition of Interleukin-18 | - Periodic fever syndromes  
- Cryopyrin-associated periodic syndromes (CAPS)  
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS)  
- Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)  
- Familial Mediterranean fever (FMF)  
- Still’s disease  
- Gout arthritis | Subcutaneous injection, 4–8 weekly depending on indication, single injection for gout arthritis |
| Ixekizumab (Taltz) | Antibody, inhibition of Interleukin-17A | - Plaque psoriasis  
- Psoriatic arthritis  
- Axial spondyloarthritis | Subcutaneous injection, 4 weekly |
| Secukinumab (Cosentyx) | Antibody, inhibition of Interleukin-17A | - Plaque psoriasis  
- Psoriatic arthritis  
- Axial spondyloarthritis | Subcutaneous injection, 4 weekly |
| Tocilizumab (RoActemra; also Sarilumab [Kevzara]) | Antibody, inhibition of Interleukin-6 | - Rheumatoid arthritis  
- Systemic juvenile idiopathic arthritis  
- Juvenile idiopathic polyarthritis  
- Giant cell arteritis (tocilizumab only) | Intravenous infusion, intervals depend on indication (tocilizumab only), or subcutaneous injection |
| Tofacitinib (Xeljanz) | Janus kinase inhibitor | - Rheumatoid arthritis  
- Psoriatic arthritis  
- Ulcerative colitis | Orally, daily |
| Ustekinumab (Stelara) | Antibody, inhibition of Interleukin-12 and Interleukin-23 | - Psoriatic arthritis  
- Plaque psoriasis  
- Crohn’s disease | Intravenous infusion or subcutaneous injection, 12 weekly |
| Vedolizumab (Entyvio) | Antibody, inhibition of α4β7 Integrin | - Ulcerative colitis  
- Crohn’s disease | Intravenous infusion, 8 weekly |
Inclusion and exclusion criteria

Studies published in English were included for in-depth analysis if any of the terms “tuberculosis”, “latent infection”, “opportunistic infection” or “opportunistic disease” were mentioned in the title of the respective publication, in the corresponding registration as a clinical study in ClinicalTrials.gov, in supplements, online study protocols or in information separately published by the sponsors. Case reports, letters, position papers, guidelines, reviews (not including original data), phase 1 studies, inadequately randomized or pooled studies in which the design was not explicitly described, animal testing, laboratory work and quality-of-life studies that had already been updated over time by continuing the existing study design were all excluded. Studies were also excluded where a TNFi was administered concurrently with the novel biologic. The supplement presents the flow diagrams of the MEDLINE search results for the biologic in question with reasons as to the inclusion and exclusion of cited studies.

Variables assessed

The following variables were recorded, if available: 1) first author, year of publication, country of origin of the first author; 2) type of study (phase 2 or phase 3, long-term study [long term extension (LTE)] or open-label [OL] with previously randomised patients); 3) criteria of project (which diseases and which target group are addressed); 4) dosage(s) of the administered biologic; 5) number of patients receiving initial treatment and completing the placebo course of treatment; 6) number of patients receiving initial treatment and completing the placebo course of treatment; 7) duration of treatment; 8) clinicalTrials.gov (NCT) identifier of the respective study (if provided); 9) tuberculosis mentioned in NCT (yes/no); 10) active tuberculosis explicitly excluded (yes/no); 11) screening for LTBI (yes/no); 12) specification of the chosen method (IGRA [QuantiFERON Gold in Tube (QFT)], T-SPOT [T-Spot.TB] or PPD-Mantoux) if LTBI screening was performed; 13) preventive chemotherapy (PT) if LTBI test positive (yes/no); 14) exclusion of potential study participants in the case of any LTBI (yes/no); 15) exclusion of potential study participants where LTBI untreated (yes/no); 16) number of LTBI patients given PT; 17) number of tuberculosis manifestation cases.

Results

677 potentially relevant citations were retrieved. (Abatacept: 92, Anakinra: 85, Apremilast: 28, Baricitinib: 16, Belimumab: 38, Canakinumab: 20, Ixekizumab: 42, Secukinumab: 57, Tocilizumab: 93, Tofacitinib: 83, Ustekinumab: 94 and Vedolizumab 29). 127 studies comprising a total of 34,293 patients received non-TNFi treatment for inclusion in the relevant trials. Absolute numbers of those LTBI patients excluded from the outset could only be found in three studies; those covered a total of 191 patients designated to be treated with baricitinib [41] or vedolizumab [131, 135].

As can be seen from Table 15S, a notable variety of exclusionary criteria was employed in respect to patients’ LTBI treatment status, which further complicated the comparison of the TB risk introduced by the biologics.

Of note, a tendency for increased refinement of LTBI screening prior to inclusion in a study is observable among more recent studies. For example, before the administration of tofacitinib, Winthrop and coworkers [109] stipulated that the MDR-TB status of LTBI-positive candidates home countries be verified. Only those patients coming from low MDR countries (MDR-TB < 5% of all tuberculosis cases) could be accepted for the study. This was intended to ensure that a diagnosis of LTBI would most likely relate to an INH-susceptible index case and that the subsequent INH therapy would also be effective prior to administration of the biologic.

The absolute number of patients who eventually received PT was only provided in two studies, one on treatment with ixekizumab (n = 22) [60] and one on treatment with ustekinumab (n = 154) [121, 127, 129].

Discussion

The relative risk for TB following TNFi therapy has been extensively reviewed and is clearly increased, depending on the clinical setting and the TNFi used. Here we address whether similar risks are to be assumed for immune inhibitors not targeting TNF. In a recently published “umbrella” review comprising thirteen meta-analyses of patients with immune-mediated inflammatory diseases treated with TNFi the relative risk of developing TB in randomized trials more than doubled the relative risk ratio (RR 2.057, 95% confidence interval 1.70 to 2.50) compared to patients of the (placebo) control groups [135] while in observational studies – dependent on the clinical setting and...
the drug used – an increase of the risk up to 25 times was reported [136].

As our analysis finds only 24 explicitly documented TB cases among the 34,293 patients treated with any non-TNFi the TB risk under non-TNFi would, at first glance, not be worth mentioning. Although patients with untreated LTBI were excluded, additional 9 TB cases are mentioned in Smolen’s [137] analysis of patients receiving baricitinib who, however, can not be assigned to specific studies.

In fact, the reported number of TB cases in the 127 studies included in this analysis does not clearly indicate a preferential risk picture for the choice of non-TNFi vs TNFi, but may more likely reflect a bias caused by the elimination or special handling of patients who tested positive (or were simply considered to have LTBI). The review cohort includes a significant number of patients who were later excluded prior to an approval study or who received a PT before or while biologics or JAKi were administered, and who therefore no longer exhibit a “natural” tuberculosis reactivation risk. A valid clarification of the overall TB risk of TNFi is further complicated by heterogeneity in studies’ strategies for PT: Differences in the timing, nature and length of PT, preclude a standardized cohort. Furthermore, because many publications do not mention opportunistic infections including TB as possible undesired events, our review can also be considered to be under-reporting the number of actual TB cases resulting from treatment with non-TNFi biologics.

To date, a few reviews on the matter of TB risk when administering non-TNFi biologics have been published. A comprehensive review performed by Cantini et al. [139], supplemented by a most recently published review on the risk of TB with Janus Kinase inhibitors tocilizumab and baricitinib [140], summarises published study results but does not provide an in-depth analysis. It concludes, on the basis of the very low number of TB cases reported, that the biologics tocilizumab, abatacept, rituximab, secukinumab and ustekinumab exhibit a very low or zero risk of provoking TB reactivation, even though it is also stated that 19 studies lacked information about LTBI screening procedures and any preventive therapy. Specifically, in relation to abatacept, it is explicitly claimed that LTBI screening was not necessary for this reason, referencing not only the controlled studies but also the absence of reactivation in the French “ORA” register study [141] and in a long-term Japanese study [142]. In fact, patients’ LTBI status was not even recorded in the “ORA” register, and the Japanese multi-centre study only enquired about prior tuberculosis disease cases. It is also unclear how many patients from approval studies who were found not to have had LTBI, or to have been treated for LTBI, were included in the Japanese study.

As regards treatment with secukinumab, Cantini et al. references the PSOLAR study [143] as evidence of the lack of tuberculosis risk. That study, too, lacks any information about LTBI screening prior to non-TNFi treatment.

Another review on this topic is the multi-chapter narrative consensus document of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH). While abatacept has not been evaluated in this regard, that review reports no reactivation risk for vedolizumab [144], and a merely theoretical risk for anakinra, canakinumab, ixekizumab, secukinumab and ustekinumab [145], but attests to a significant reactivation risk for JAK inhibitors baricitinib and tofacitinib [146] and for tocilizumab [144]. With exception of vedolizumab, LTBI screening and subsequent preventive therapy for those tested positive is likewise recommended. Regarding the risk for tocilizumab, the Winthrop study [147] is referenced, in which it is stated that LTBI testing was performed in all approval studies, usually using QFT, and that in phase 2 studies, all patients with LTBI were excluded from treatment with tocilizumab, while in phase 3 studies, all test-positive patients had begun INH treatment 4 weeks prior to the beginning of TNFi treatment.

Fowler et al. [148], in their recently published systematic review on the risk of TB reactivation under interleukin-17 inhibitor therapy (secukinumab and ixekizumab) for psoriasis, carefully explain that, wherever inclusion criteria specific to TB was provided in the 23 included studies, candidates presenting for their study with known LTBI or testing positive in their pre-study LTBI screening had either been excluded or had received preventive treatment prior to their inclusion. Not surprisingly, then, they were unable to identify any risk for TB reactivation under the following immune suppressive therapy.

Indeed, one may assume that the apparently low incidence of TB disease in patients under non-TNFi treatment is to be credited to the widespread availability and use of more specific tests (IGRAs vs Mantoux TST) and the application of those tests by clinicians evaluating and prescribing the new biologics. Thus, the dreadful experience of the rheumatology community at the advent of the biologics era (with TNFi) has apparently not been repeated.

Conclusions

According to the results of our review there is – with few exceptions – a lack of transparency regarding the prior exclusion or prior treatment of patients with LTBI in randomised studies of non-TNFi biologics. Thus, to date, it is not possible to make a valid statement about the actual risk of LTBI reactivation under treatment with those novel biologics and JAKi compared to TNF-alpha inhibitors. However, even under consideration of the caveats mentioned above, the risk appears to be generally smaller for non-TNFi biologics.

We conclude that – also in line with the recommendations of the German Society for Rheumatology (DGRh) [149] – the existing recommendations of the German Central Committee against Tuberculosis [4] should be applied for patients under consideration for non-TNFi biologics and JAKi, in the same way as is done prior to administering TNF-alpha inhibitors. This shall also apply to bDMARDs, tsDMARDs or other immunosuppressants upon approval in the future, irrespective of the underlying effective mechanisms. The only exception here comes when the required safety studies can claim that patients with LTBI were not excluded nor preventively treated and that there was no evidence of drug-induced TB reactivation. This means that patients should be regularly screened for LTBI before commencing therapy and, in the event of a positive IGRA test, PT should be administered for at least 4 weeks before the start of...
therapy. As a 4-month regimen of rifampin is not inferior to the 9-month regimen of INH, but is associated with a higher rate of treatment completion and lower toxicity [149], rifampicin may be preferred. Recent studies [151, 152] have demonstrated that annual or otherwise serial LTBI screening of patients taking biologics is not generally required and may be better limited to a subset of high-risk patients. These can be identified by a careful review of TB exposure risk factors of patients on biologics at each clinic visit. This is in line with a post-hoc analysis of integrated safety data from 7016 ixekizumab-treated patients (5898 with psoriasis, 1118 with psoriasis arthropathy), of which only 101 (1.7%) who initially tested negative for LTBI emerged with LTBI (means of 1010 and 596 days, respectively) under treatment [153].

Further long-term “real world” register studies on tuberculosis progression risk in relation to individual substances (for IGRA-positive cases without preventive therapy) would have to be done to reach a conclusive assessment of the progression risk of non-TNFi biologics. On the basis of such data, it would then be possible to determine the individual risk of TB reactivation and weight it against the occurrence of possible side effects of PT. Responsible extension of the TNFi recommendation and weight it against the occurrence of possible side effects of PT. Responsible extension of the TNFi recommendations to non-TNFi as recommended here, however, will presumably preclude the human suffering such studies would imply.

Conflict of interest

R. D. received a grant by the Niedersächsischer Verein zur Bekämpfung der Tuberkulose, Lungen- und Bronchialerkrankungen. M. F. has worked as a paid consultant or speaker for the following companies: Novartis, LEO Pharma, Almirall and AbbVie.

C. K. has consulted or lectured for AbbVie, Centogene, Celltrion, Chugai, Gilead, GSK, Janssen, Lilly, Medac, MSD, Novartis, Pfizer, Roche, Sanofi and UCB.

U. M. has been a paid consultant and/or speaker and/or recipient of research support and/or participant in clinical trials for AbbVie, Almirall, Eli Lilly, Formycon, Janssen, LEO Pharma and Novartis.

R. O.-K. has received fees from Novartis, Gilead, Boehringer Ingelheim, Berlin Chemie, Insmed and Astra Zeneca for lectures that were financially supported or organized by the companies mentioned.


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