Medizinische Universität Graz

KAGes

Infektionen der Lunge (TBC u.a.) bei rheumatischen Erkrankungen

in 20 min (+5 min Diskussion)

"Rheuma im Spannungsfeld Lunge / Herz / Darmtrakt / Haut“
22.06.2017
Klagenfurt

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KAGes

Conflict of Interest

Actavis, Astellas, AOP, Bayer, Boehringer Ingelheim, BMS, Cellestis, Chiesi, GSK, MSD, Novartis, Oxford Immunotec, Pfizer, Roche, Sandoz

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BEGRIFFLICHKEITEN

EULAR recommendations for the management of rheumatoid arthritis : 2016 update

- **csDMARD**: conventional synthetic DMARD
  - methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
- **bDMARD**: biological DMARD
  - TNF-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
  - interleukin 6 antagonist (tocilizumab)
  - anti-CD28 = T-cell co-stimulation blockade (abatacept)
  - anti-B cell = B-cell depletion (rituximab)
  - clazakizumab, sarilumab and sirukumab
  - Interleukin 12/23 inhibitor (ustekinumab)
- **bsDMARD**: biosimilar DMARD
- **tsDMARD**: targeted synthetic DMARD
  - Janus kinase inhibitors (tofacitinib, baricitinib)
  - Phosphodiesterase-4 inhibition (premilast)

Rot: analysiert in „Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis“ Lancet 2015; 386: 258–65

Smolen JS, et al. Ann Rheum Dis 2017;0:1–18.

Therapie von rheumatologischen Erkrankungen und Infektionsrisiko

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care Program

Comparative Effectiveness Review
Number 55

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

AHRQ Publication No. 12-EHC025-EF Updated June 2012

Infektionsrisiko erhöht durch Steroide

Table 39. Infection in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et al., 2007[218]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Glucocorticoids	The risk for all infections requiring hospitalization was most elevated with glucocorticoid agents (RR, 2.6; 95% CI, 2.3 to 2.9); Similar effects were seen with pneumonia as the outcome (RR, 2.1; 95% CI, 2.4 to 3.1).	Fair
*Brassard et al., 2006[219]	Retrospective cohort study 112,300 Up to 5 years	RA pts from PharMetrics data (U.S.)	Several oral DMARDs, biologic DMARDs, corticosteroids	Adjusted rate ratio of developing TB with corticosteroids: 1.7 (95% CI, 1.3 to 2.2).	Fair
Doran et al., 2002[220]	Retrospective cohort 609 39 years	RA patients	Several oral DMARDs, corticosteroids	In patients hospitalized for infection, corticosteroid use increased risk (HR, 1.56; 95% CI, 1.20 to 2.04)	Fair
*Lacaille et al., 2008[221]	Retrospective cohort 27,710 162,720 person years	Pts with RA from British Columbia, Canada	Oral DMARDs, corticosteroids	Adjusted Rate Ratio for serious infections: DMARDs+corticosteroids:1.63 (95% CI, 1.5 to 1.77); corticosteroids alone: 1.9 (95% CI, 1.75 to 2.05)	Fair
*Greenberg et al., 2010[226] CORRONA	Prospective cohort 7,971 15,047 person-years	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	MTX, oral DMARDs, anti-TNF agents, PRED	Adjusted incidence rate ratio of infection and opportunistic infection for PRED compared with oral DMARDs, respectively: IRR 1.05 (0.97-1.15, *P*=0.251); IRR 1.63 (1.20-2.21, *P*=0.002) PRED above 10 mg daily associated with risk of infection (IRR 1.30, 95% 1.11-1.53, *P*=0.001)	Fair
*Schneeweiss et al., 2007[222]	Retrospective cohort 15,597 Up to 8 years	Medicare beneficiaries ages 65 and older with RA	Glucocorticoids	Compared with MTX use, glucocorticoid use associated with serious bacterial infections (RR, 2.25; 95% CI, 1.57 to 3.22)	Fair
*Smitten et al., 2008[223]	Retrospective cohort 24,530 26.6 months	RA pts from PharMetrics data (U.S.)	Corticosteroids	Oral corticosteroid use increased risk of hospitalized infection (RR, 1.92; 95% CI, 1.67 to 2.21). Risk increased with dose.	Good
*Smitten et al., 2007[224]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	RA pts from PM database and UK GPRD	Corticosteroids	Risk of herpes zoster infection with corticosteroids only: (PM: OR, 2.51; 95% CI, 2.05 to 3.06 GPRD: 1.46; 95% CI, 1.24 to 1.70)	Fair

Infektionsrisiko erhöht durch csDMARDs

Table 44. Infection in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et al., 2007[218]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Oral DMARDs including: MTX, LEF, HCQ, SSZ	Relative risk for infections requiring hospitalization: MTX 1.10 (95% CI, 0.98 to 1.23); all other DMARDs (includes LEF, SSZ) 0.99 (95% CI, 0.84 to 1.16); Antimalarial (includes HCQ) 1.06 (95% CI, 0.92 to 1.22)	Fair
*Brassard et al., 2009[238]	Retrospective cohort study 24,282 1980-2003 for cohort and 1992-2003 for TB incidence rates	RA pts from Quebec	Traditional DMARDs including MTX and LEF, corticosteroids	Rate ratio of TB associated with any DMARD use: 3.0 (95% CI, 1.6 to 5.8).	Fair
*Brassard et al., 2006[219]	Retrospective cohort study 112,300 Up to 5 years	RA pts from the PharMetrics Patient-Centric database	Several oral DMARDs, biologic DMARDs, corticosteroids	Adjusted rate ratio of developing TB with use of traditional DMARDs: 1.2 (95% CI, 1.0 to 1.5).	Fair
Cannon et al., 2004[229]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Respiratory infection: LEF 20/1,000 PY, MTX 38.9/1,000 PY, Other 36.9/1,000 PY	Fair
Doran et al., 2002[220]	Retrospective cohort 609 39 years	RA pts	Several oral DMARDs, corticosteroids	Compared with oral DMARDs, corticosteroids increased risk of hospitalized infection (HR, 1.56; 95% CI, 1.20 to 2.04)	Fair
*Greenberg et al., 2010[226] CORRONA	Prospective cohort 7,971 15,047 patient years	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	MTX, oral DMARDs, anti-TNF agents, PRED	Adjusted incidence rate ratio (IRR) for infections: MTX (IRR, 1.30; 95% CI, 1.12 to 1.50, *P*<0.001) Adjusted incidence rate ratio (IRR) for opportunistic infections: MTX (IRR, 0.93; 95% CI, 0.54 to 1.60, *P*=0.781)	Fair
*Grijalva et al., 2010[240]	Prospective cohort 28,906 3 years	Tennesee Medicaid-enrolled RA pts initiating DMARD use	MTX, LEF, SSZ, HCQ, biologic DMARDs, glucocorticoids	Compared with MTX; LEF, SSZ or HCQ did not increase risks of hospitalizations due to pneumonia or serious infections	Good
*Lacaille et al., 2008[221]	Retrospective cohort 27,710 162,720 person years	Pts with RA from British Columbia, Canada	Oral DMARDs, corticosteroids	Adjusted rate ratio for serious infections: DMARDs+corticosteroids:1.63 (95% CI, 1.5 to 1.77); DMARDs alone: 0.92 (95% CI, 0.85 to 1.0)	Fair

Table 44. Infection in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*McDonald et al., 2009[239]	Retrospective cohort 20,357 7 years	Pts with RA in the Veterans Affairs health care system	Traditional DMARDs	No increased risk of infection with oral DMARDs; SSZ associated with a lower risk of herpes zoster infection (HR, 0.44; 95% CI, 0.21 to 0.91)	Fair
*Smitten et al., 2008[223]	Retrospective cohort 24,530 26.6 months	Pts with RA from U.S. PharMetrics data	MTX, LEF, HCQ, SSZ	MTX and HCQ decreased risk of hospitalized infection (RR, 0.81; 95% CI, 0.70 to 0.93; RR, 0.74; 95% CI, 0.62 to 0.89; respectively).	Good
*Smitten et al., 2007[224]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	Pts with RA the PM database and UK GPRD	Corticosteroids, traditional DMARDs, biologic DMARDs	Risk of herpes zoster infection with traditional DMARDs alone (PM: OR,1.37; 95% CI, 1.18 to 1.59; GPRD, 1.27; 95% CI, 1.10 to 1.48)	Fair
Wolfe et al., 2006[237]	Prospective cohort 16,788 3.5 years	RA diagnosis	PRED, LEF, SSZ, MTX, ETA, INF, ADA	Risk for hospitalization for pneumonia: PRED HR, 1.7 (95% CI, 1.5 to 2.1), LEF HR, 1.3 (95% CI, 1.0 to 1.5). No significant differences for SSZ, MTX	Fair

* New study added since last review.

ADA = adalimumab; AERS = adverse events reporting system; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GI = gastrointestinal; GPRD = General Practict Research Database; HCQ = hydroxychloroquine; HR = hazard ratio; INF = infliximab; LEF = leflunomide; MTX = methotrexate; N/A = not applicable; NR = not reported; OR = odds ratio; PM = PharMetrics; PNL = prednisolone; PRED = prednisone; Pts = patients; PY = person years; RA = rheumatoid arthritis; RR = rate ratio; SSZ = sulfasalazine; TB = tuberculosis

Infektionsrisiko erhöht durch „Biologika

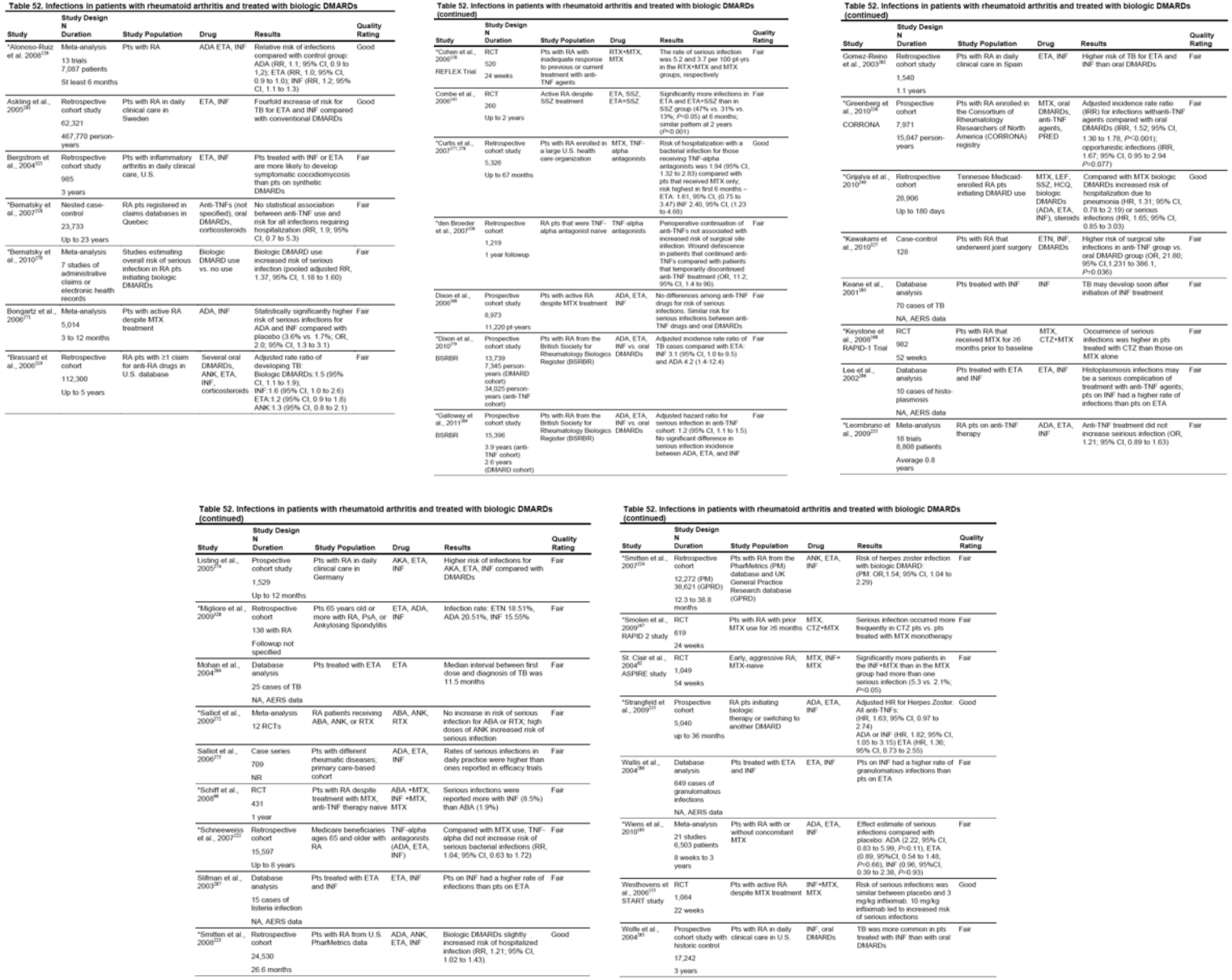


Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Alonoso-Ruiz et al. 2008[124]	Meta-analysis 13 trials 7,087 patients St least 6 months	Pts with RA	ADA ETA, INF	Relative risk of infections compared with control group: ADA (RR, 1.1; 95% CI, 0.9 to 1.2); ETA (RR, 1.0; 95% CI, 0.9 to 1.0); INF (RR, 1.2; 95% CI, 1.1 to 1.3)	Good
Askling et al., 2005[282]	Retrospective cohort study 62,321 467,770 person-years	Pts with RA in daily clinical care in Sweden	ETA, INF	Fourfold increase of risk for TB for ETA and INF compared with conventional DMARDs	Good
Bergstrom et al., 2004[325]	Retrospective cohort study 985 3 years	Pts with inflammatory arthritis in daily clinical care, U.S.	ETA, INF	Pts treated with INF or ETA are more likely to develop symptomatic coccidiomycosis than pts on synthetic DMARDs	Fair
*Bernatsky et al., 2007[119]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Anti-TNFs (not specified), oral DMARDs, corticosteroids	No statistical association between anti-TNF use and risk for all infections requiring hospitalization (RR, 1.9; 95% CI, 0.7 to 5.3)	Fair
*Bernatsky et al., 2010[176]	Meta-analysis 7 studies of administrative claims or electronic health records	Studies estimating overall risk of serious infection in RA pts initiating biologic DMARDs	Biologic DMARD use vs. no use	Biologic DMARD use increased risk of serious infection (pooled adjusted RR, 1.37, 95% CI, 1.18 to 1.60)	Fair
Bongartz et al., 2006[171]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of serious infections for ADA and INF compared with placebo (3.6% vs. 1.7%; OR, 2.0; 95% CI, 1.3 to 3.1)	Fair
*Brassard et al., 2006[219]	Retrospective cohort 112,300 Up to 5 years	RA pts with ≥1 claim for anti-RA drugs in U.S. database	Several oral DMARDs, ANK, ETA, INF, corticosteroids	Adjusted rate ratio of developing TB: Biologic DMARDs:1.5 (95% CI, 1.1 to 1.9); INF:1.6 (95% CI, 1.0 to 2.6) ETA:1.2 (95% CI, 0.9 to 1.8) ANK:1.3 (95% CI, 0.8 to 2.1)	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Cohen et al., 2006[128] REFLEX Trial	RCT 520 24 weeks	Pts with RA with inadequate response to previous or current treatment with anti-TNF agents	RTX+MTX, MTX	The rate of serious infection was 5.2 and 3.7 per 100 pt-yrs in the RTX+MTX and MTX groups, respectively	Fair
Combe et al., 2006[143]	RCT 260 Up to 2 years	Active RA despite SSZ treatment	ETA, SSZ, ETA+SSZ	Significantly more infections in ETA and ETA+SSZ than in SSZ group (47% vs. 31% vs. 13%; $P<0.05$) at 6 months; similar pattern at 2 years ($P<0.001$)	Fair
*Curtis et al., 2007[175,176]	Retrospective cohort study 5,326 Up to 67 months	Pts with RA enrolled in a large U.S. health care organization	MTX, TNF-alpha antagonists	Risk of hospitalization with a bacterial infection for those receiving TNF-alpha antagonists was 1.94 (95% CI, 1.32 to 2.83) compared with pts that received MTX only; risk highest in first 6 months – ETA: 1.61, 95% CI, (0.75 to 3.47) INF 2.40, 95% CI, (1.23 to 4.68)	Good
*den Broeder et al., 2007[134]	Retrospective cohort 1,219 1 year followup	RA pts that were TNF-alpha antagonist naive	TNF-alpha antagonists	Perioperative continuation of anti-TNFs not associated with increased risk of surgical site infection. Wound dehiscence in patients that continued anti-TNFs compared with patients that temporarily discontinued anti-TNF treatment (OR, 11.2; 95% CI, 1.4 to 90).	Fair
Dixon et al., 2006[268]	Prospective cohort study 8,973 11,220 pt-years	Pts with active RA despite MTX treatment	ADA, ETA, INF	No differences among anti-TNF drugs for risk of serious infections. Similar risk for serious infections between anti-TNF drugs and oral DMARDs	Fair
*Dixon et al., 2010[278] BSRBR	Prospective cohort study 13,739 7,345 person-years (DMARD cohort) 34,025 person-years (anti-TNF cohort)	Pts with RA from the British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF vs. oral DMARDs	Adjusted incidence rate ratio of TB cases compared with ETA: INF 3.1 (95% CI, 1.0 to 9.5) and ADA 4.2 (1.4-12.4)	Fair
*Galloway et al., 2011[146] BSRBR	Prospective cohort study 15,396 3.9 years (anti-TNF cohort) 2.6 years (DMARD cohort)	Pts with RA from the British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF vs. oral DMARDs	Adjusted hazard ratio for serious infection in anti-TNF cohort: 1.2 (95% CI, 1.1 to 1.5). No significant difference in serious infection incidence between ADA, ETA, and INF	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Gomez-Reino et al., 2003[382]	Retrospective cohort study 1,540 1.1 years	Pts with RA in daily clinical care in Spain	ETA, INF	Higher risk of TB for ETA and INF than oral DMARDs	Fair
*Greenberg et al., 2010[258] CORRONA	Prospective cohort 7,971 15,047 person-years	Pts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry	MTX, oral DMARDs, anti-TNF agents, PRED	Adjusted incidence rate ratio (IRR) for infections withanti-TNF agents compared with oral DMARDs (IRR, 1.52; 95% CI, 1.30 to 1.78, $P<0.001$); opportunistic infections (IRR, 1.67; 95% CI, 0.95 to 2.94 $P=0.077$)	Fair
*Grijalva et al., 2010[288]	Retrospective cohort 28,906 Up to 180 days	Tennesee Medicaid-enrolled RA pts initiating DMARD use	MTX, LEF, SSZ, HCQ, biologic DMARDs (ADA, ETA, INF), steroids	Compared with MTX biologic DMARDs increased risk of hospitalization due to pneumonia (HR, 1.31; 95% CI, 0.78 to 2.19) or serious infections (HR, 1.65; 95% CI, 0.85 to 3.03)	Good
*Kawakami et al., 2010[337]	Case-control 128	Pts with RA that underwent joint surgery	ETN, INF, DMARDs	Higher risk of surgical site infections in anti-TNF group vs. oral DMARD group (OR, 21.80; 95% CI,1.231 to 386.1, $P=0.036$)	Fair
Keane et al., 2001[283]	Database analysis 70 cases of TB NA, AERS data	Pts treated with INF	INF	TB may develop soon after initiation of INF treatment	Fair
*Keystone et al., 2008[148] RAPID-1 Trial	RCT 982 52 weeks	Pts with RA that received MTX for ≥6 months prior to baseline	MTX, CTZ+MTX	Occurrence of serious infections was higher in pts treated with CTZ than those on MTX alone	Fair
Lee et al., 2002[284]	Database analysis 10 cases of histo-plasmosis NA, AERS data	Pts treated with ETA and INF	ETA, INF	Histoplasmosis infections may be a serious complication of treatment with anti-TNF agents; pts on INF had a higher rate of infections than pts on ETA	Fair
*Leombruno et al., 2009[233]	Meta-analysis 18 trials 8,868 patients Average 0.8 years	RA pts on anti-TNF therapy	ADA, ETA, INF	Anti-TNF treatment did not increase serious infection (OR, 1.21; 95% CI, 0.89 to 1.63)	Fair

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

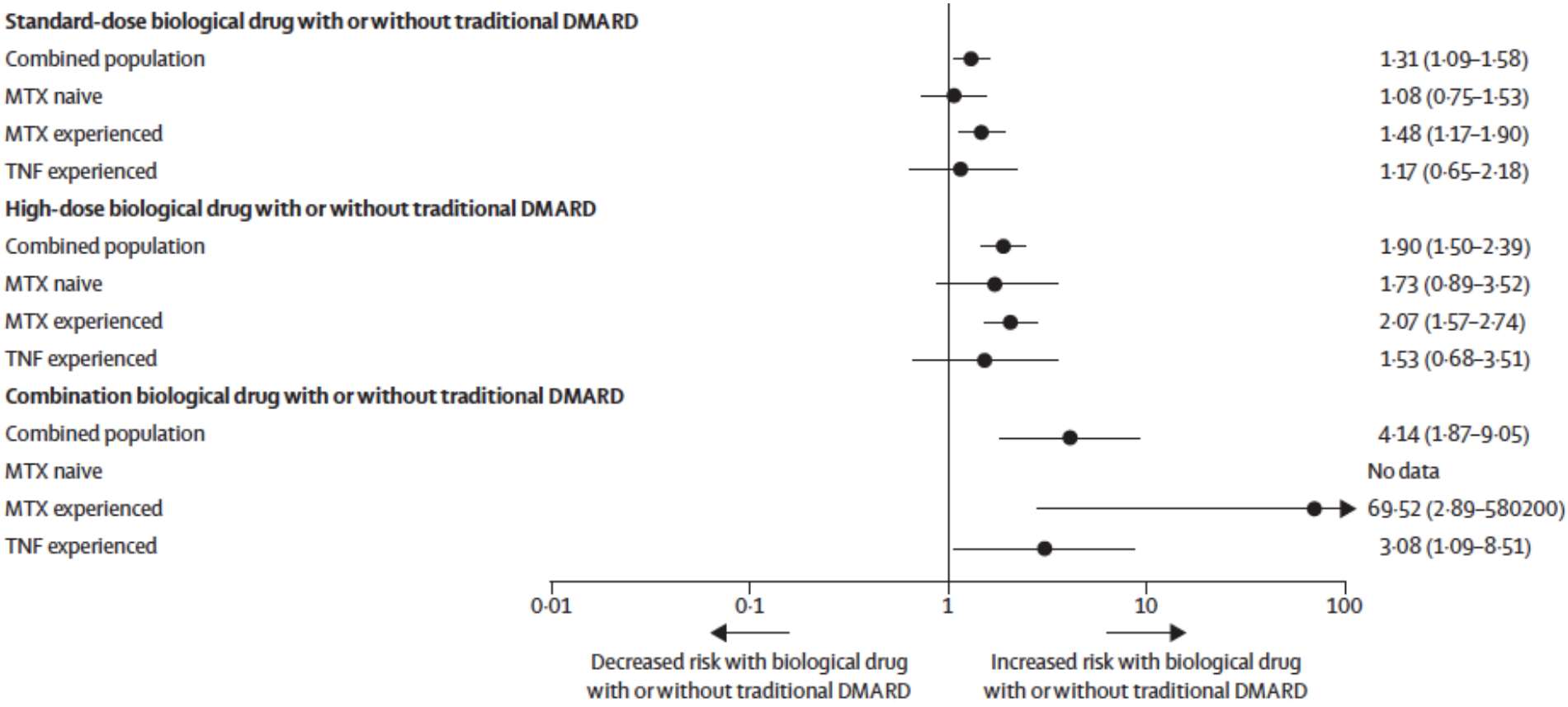
Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Listing et al., 2005[274]	Prospective cohort study 1,529 Up to 12 months	Pts with RA in daily clinical care in Germany	AKA, ETA, INF	Higher risk of infections for AKA, ETA, INF compared with DMARDs	Fair
*Migliore et al., 2009[218]	Retrospective cohort 138 with RA Followup not specified	Pts 65 years old or more with RA, PsA, or Ankylosing Spondylitis	ETA, ADA, INF	Infection rate: ETN 18.51%, ADA 20.51%, INF 15.55%	Fair
Mohan et al., 2004[264]	Database analysis 25 cases of TB NA, AERS data	Pts treated with ETA	ETA	Median interval between first dose and diagnosis of TB was 11.5 months	Fair
*Salliot et al., 2009[232]	Meta-analysis 12 RCTs	RA patients receiving ABA, ANK, or RTX	ABA, ANK, RTX	No increase in risk of serious infection for ABA or RTX; high doses of ANK increased risk of serious infection	Fair
Salliot et al., 2006[275]	Case series 709 NR	Pts with different rheumatic diseases; primary care-based cohort	ADA, ETA, INF	Rates of serious infections in daily practice were higher than ones reported in efficacy trials	Fair
*Schiff et al., 2008[96]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA +MTX, INF +MTX, MTX	Serious infections were reported more with INF (8.5%) than ABA (1.9%)	Fair
*Schneeweiss et al., 2007[222]	Retrospective cohort 15,597 Up to 8 years	Medicare beneficiaries ages 65 and older with RA	TNF-alpha antagonists (ADA, ETA, INF)	Compared with MTX use, TNF-alpha did not increase risk of serious bacterial infections (RR, 1.04; 95% CI, 0.63 to 1.72)	Fair
Silfman et al., 2003[267]	Database analysis 15 cases of listeria infection NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of infections than pts on ETA	Fair
*Smitten et al., 2008[223]	Retrospective cohort 24,530 26.6 months	Pts with RA from U.S. PharMetrics data	ADA, ANK, ETA, INF	Biologic DMARDs slightly increased risk of hospitalized infection (RR, 1.21; 95% CI, 1.02 to 1.43).	Good

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Smitten et al., 2007[224]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	Pts with RA from the PharMetrics (PM) database and UK General Practice Research database (GPRD)	ANK, ETA, INF	Risk of herpes zoster infection with biologic DMARD: (PM: OR,1.54; 95% CI, 1.04 to 2.29)	Fair
*Smolen et al., 2009[261] RAPID 2 study	RCT 619 24 weeks	Pts with RA with prior MTX use for ≥6 months	MTX, CTZ+MTX	Serious infection occurred more frequently in CTZ pts vs. pts treated with MTX monotherapy	Fair
St. Clair et al., 2004[42] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive	MTX, INF+ MTX	Significantly more patients in the INF+MTX than in the MTX group had more than one serious infection (5.3 vs. 2.1%; $P<0.05$)	Fair
*Strangfeld et al., 2009[233]	Prospective cohort 5,040 up to 36 months	RA pts initiating biologic therapy or switching to another DMARD	ADA, ETA, INF	Adjusted HR for Herpes Zoster. All anti-TNFs: (HR, 1.63; 95% CI, 0.97 to 2.74) ADA or INF (HR, 1.82; 95% CI, 1.05 to 3.15) ETA (HR, 1.36; 95% CI, 0.73 to 2.55)	Good
Wallis et al., 2004[280]	Database analysis 649 cases of granulomatous infections NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of granulomatous infections than pts on ETA	Fair
*Wiens et al., 2010[181]	Meta-analysis 21 studies 6,503 patients 8 weeks to 3 years	Pts with RA with or without concomitant MTX	ADA, ETA, INF	Effect estimate of serious infections compared with placebo: ADA (2.22, 95% CI, 0.83 to 5.99, $P=0.11$), ETA (0.89, 95%CI, 0.54 to 1.48, $P=0.66$), INF (0.96, 95%CI, 0.39 to 2.38, $P=0.93$)	Fair
Westhovens et al., 2006[155] START study	RCT 1,084 22 weeks	Pts with active RA despite MTX treatment	INF+MTX, MTX	Risk of serious infections was similar between placebo and 3 mg/kg infliximab. 10 mg/kg infliximab led to increased risk of serious infections	Good
Wolfe et al., 2004[380]	Prospective cohort study with historic control 17,242 3 years	Pts with RA in daily clinical care in U.S.	INF, oral DMARDs	TB was more common in pts treated with INF than with oral DMARDs	Fair

Infekt-Risiko: Biologika > csDMARD (und dosisabhängig)

Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis (2015)



Compared with traditional DMARDs, standard-dose biological drugs (OR 1.31, 95% credible interval [CrI] 1.09–1.58) and high-dose biological drugs (1.90, 1.50–2.39) were associated with an increased risk of serious infections ...

Jasvinder A Singh et al. Lancet 2015; 386: 258–65

Infekt-Risiko: Inflix > Ada = Ritux >Aba (und altersabhängig)

Risk of Hospitalized Bacterial Infections Associated with Biologic Treatment Among U.S. Veterans with Rheumatoid Arthritis

Infection-Related Risk Factor	Hazard Ratio (95% CI)
Medication Exposure (referent to etanercept)	
Adalimumab	1.4 (0.9 – 2.2)
Infliximab	2.3 (1.3 – 4.0)
Abatacept	1.1 (0.6–2.1)
Rituximab	1.4 (0.8–2.6)
Age Group (years) (referent to <50)	
50 ≤ 70	2.8 (1.4–5.4)
≥ 70	2.7 (1.3–5.9)

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2016 October 12.

Infekt-Risiko: Inflix > Ada > Eta

Infections With Biologics in Rheumatoid Arthritis and Related Conditions: a Scoping Review of Serious or Hospitalized Infections in Observational Studies

Table 5 Results of the Cox proportional hazard model of the risk of serious infection using data from van Dartel et al. [20]

	Hazard ratio	95 % CI
Etanercept	Reference	
Adalimumab	1.83	1.49–2.26
Infliximab	2.04	1.62–2.58
Age	1.04	1.02–1.04
DAS28 (time-dependent)	1.21	1.13–1.29
Year of starting anti-TNF therapy	0.99	0.95–1.03
Comorbidities	1.73	1.40–2.13

Age, year of starting anti-TNF therapy and comorbidities were measured at baseline and were considered as confounders

Adapted from Table 2 of van Dartel et al. [20] with permission from BMJ Publishing Group Ltd

DAS28 disease activity score of 28 joints, measured over time (time-dependent), *TNF* tumor necrosis factor

Curr Rheumatol Rep (2016) 18: 61

Infekt-Risiko: Inflix > Certo > andere Biologika

Risk of Subsequent Infection Among Patients Receiving TNF Inhibitors and Other Disease-Modifying Antirheumatic Drugs

Table 3. Multivariable analysis of the risk of infection, using the full model*

No current systemic treatment	0.74 (0.67–0.82)
Current treatment	
Nonbiologic DMARD only	Reference
Etanercept + nonbiologic DMARD	0.84 (0.73–0.97)
Etanercept only	0.92 (0.81–1.04)
Adalimumab + nonbiologic DMARD	0.91 (0.78–106)
Adalimumab only	0.93 (0.80–1.09)
Certolizumab + nonbiologic DMARD	1.41 (0.85–2.36)
Certolizumab only	1.01 (0.52–1.96)
Golimumab + nonbiologic DMARD	0.85 (0.50–1.44)
Golimumab only	0.68 (0.34–1.36)
Infliximab + nonbiologic DMARD	0.86 (0.73–1.01)
Infliximab only	1.11 (0.93–1.32)
Abatacept + nonbiologic DMARD	0.92 (0.71–1.18)
Abatacept only	0.85 (0.62–1.17)
Rituximab + nonbiologic DMARD	1.00 (0.72–1.39)
Rituximab only	0.64 (0.39–1.05)
Tocilizumab + nonbiologic DMARD	0.41 (0.17–0.99)
Tocilizumab only	0.74 (0.33–1.66)
Ustekinumab	0.48 (0.24–0.98)

Neil A. Accortt et al. ARTHRITIS & RHEUMATOLOGY, Vol. 68, No. 1, January 2016, pp 67–76

Infekt-Risiko: Rituxi > Inflix > andere Biologika

Comparative Risk of Hospitalized Infection Associated With Biologic Agents in RA Patients Enrolled in Medicare

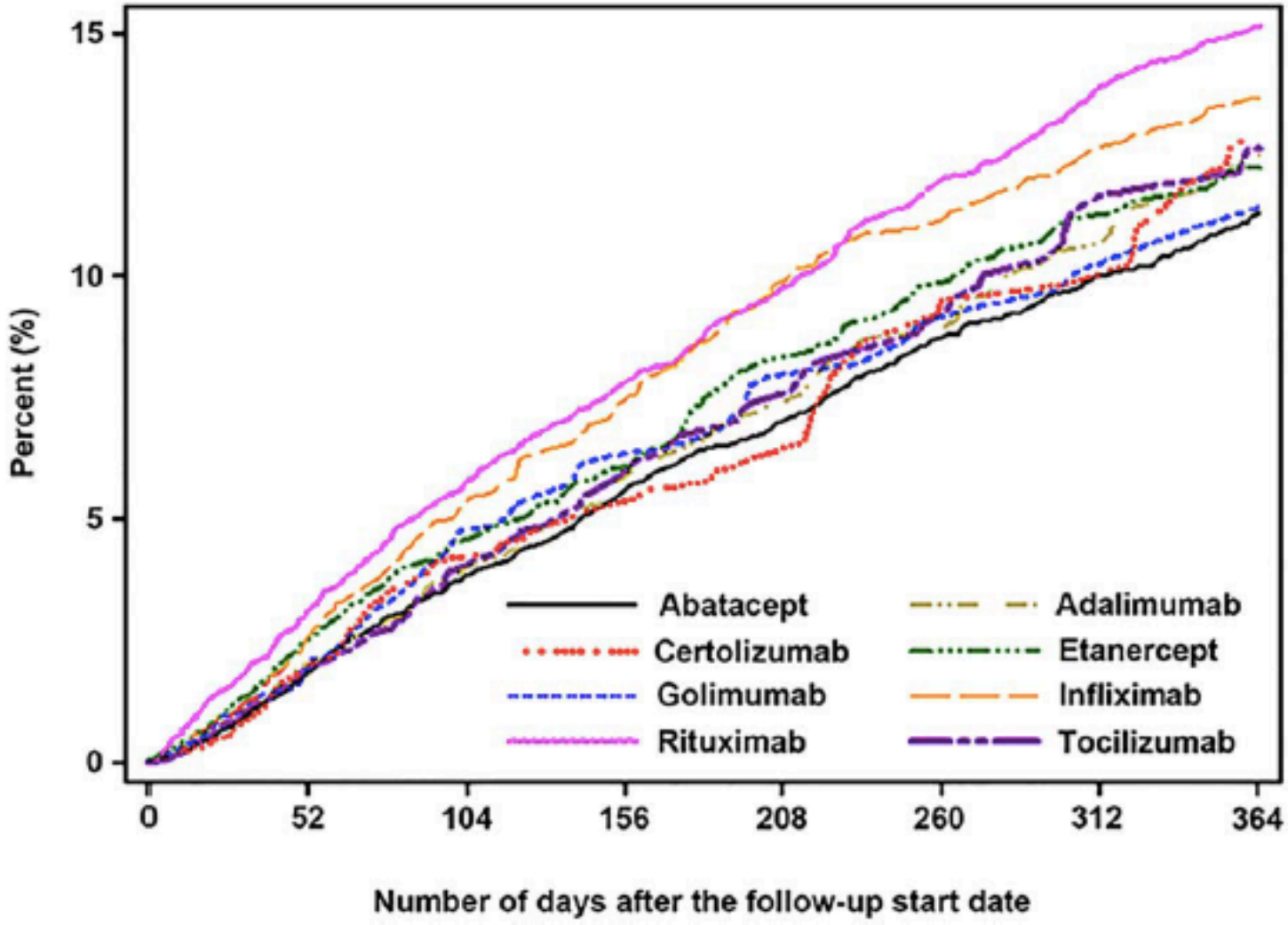


Figure 2. Cumulative incidence of hospitalized infection during 1-year followup, according to biologic agent.

Huifeng Yun et al. ARTHRITIS & RHEUMATOLOGY Vol. 68, No. 1, January 2016, pp 56–66

Infekt-Risiko: hoch bei > 7,5 mg/d Pred und bei COPD

Risk of Hospitalized Bacterial Infections Associated with Biologic Treatment Among U.S. Veterans with Rheumatoid Arthritis

Infection-Related Risk Factor	Hazard Ratio (95% CI)
COPD	1.8 (1.2–2.7)
Body Mass Index	
BMI (<20) (referent to 20–25)	1.9 (0.9–3.8)
BMI (>25) (referent to 20–25)	0.8 (0.6–1.1)
Prednisone-equivalent steroid dose (referent to no use)	
1 – 7.5 mg/day	1.3 (0.9–1.9)
> 7.5mg/day	1.8 (1.3–2.6)

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2016 October 12.

Infekt-Risiko: geringer bei Pat. mit Psoriasis o. AS

Risk of Subsequent Infection Among Patients Receiving TNF Inhibitors and Other Disease-Modifying Antirheumatic Drugs

Rheumatoid arthritis diagnosis	1.22 (1.07–1.38)
Psoriasis diagnosis	1.03 (0.92–1.16)
Psoriatic arthritis diagnosis	0.91 (0.81–1.01)
Ankylosing spondylitis diagnosis	1.11 (0.96–1.28)
Diabetes diagnosis	1.27 (1.19–1.36)
COPD diagnosis	1.37 (1.28–1.47)
Chronic liver disease diagnosis	1.12 (0.94–1.34)
Ulcer diagnosis	1.68 (1.36–2.07)
Baseline medical device use	1.05 (0.96–1.16)
Baseline corticosteroid use	1.26 (1.19–1.34)

Neil A. Accortt et al. ARTHRITIS & RHEUMATOLOGY, Vol. 68, No. 1, January 2016, pp 67–76

Infekte unter Biologika: Pneumonie > HWI > Sepsis > Haut

Comparative Risk of Hospitalized Infection Associated With Biologic Agents in RA Patients Enrolled in Medicare

Table 3. Type of infection, number of hospitalized infections, and mortality associated with different biologic agents*

	Adalimumab	Certolizumab	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Abatacept
Total no. of infections†	397	116	336	99	472	643	134	926
Septicemia/bacteremia	15.6	19.8	18.8	15.2	16.7	17.3	18.7	15.4
Pneumonia/upper respiratory tract infection	31.7	30.2	31.3	32.3	35.2	35.9	32.1	29.9
Skin and soft tissue infection	12.9	10.3	11.9	9.1	10.8	10.9	13.4	12.9
Genitourinary tract infection	26.5	29.3	26.2	35.4	24.4	21.8	22.4	28.8
Other	10.5	8.8	10.2	12.6	10.7	11.7	12.7	12.9
Length of hospital stay for serious infection, mean ± SD days	8.9 ± 10.4	10.8 ± 13.8	10.6 ± 12.0	9.5 ± 17.8	11.1 ± 15.9	9.1 ± 9.1	10.0 ± 13.1	9.2 ± 11.3
Mortality during or within 30 days after hospitalization	5.3	7.8	4.5	4.0	5.1	4.5	5.9	5.7

* Except where indicated otherwise, values are the percent.
† The total number of infections is greater than the total number of outcome events shown in Table 2, because patients can experience multiple types of infection during a single hospitalization.

Huifeng Yun et al. ARTHRITIS & RHEUMATOLOGY Vol. 68, No. 1, January 2016, pp 56–66

Infekte unter Biologika: Pneumonie > HWI > Sepsis > Haut

Infections With Biologics in Rheumatoid Arthritis and Related Conditions: a Scoping Review of Serious or Hospitalized Infections in Observational Studies

Table 2 Incidence rates of hospitalized and serious infections (per 100,000 person-years) (number of cases are shown in parentheses) with data from Smitten et al. [17]

Hospitalized infection	Non-RA[a] Incidence rates/100,000 (# cases)	RA
Overall	1679.6 (11,977)	3864.3 (1993)
Pneumonia	362.4 (2261)	841.5 (434)
Urinary tract	258.2 (1574)	484.7 (250)
Skin	171.9 (1348)	498.3 (257)
Sepsis	153.1 (972)	383.9 (198)
Opportunistic[b]	23.02 (132)	65.92 (34)
Tuberculosis	9.48 (49)	21.33 (11)
Serious[c]	3597.6 (26,523)	6028.3 (3010)

Curr Rheumatol Rep (2016) 18: 61

Infekte unter Biologika: Pneumonie > HWI > Sepsis > Haut

Infections With Biologics in Rheumatoid Arthritis and Related Conditions: a Scoping Review of Serious or Hospitalized Infections in Observational Studies

Table 1 Objectively confirmed infections in 609 rheumatoid arthritis (RA) and 609 non-RA subjects[a] with data from Doran et al. [16]

Patients, no.			Infections, no.		Incidence/100 person-years			
Infection type	RA	Non-RA	RA	Non-RA	RA	Non-RA	Rate ratio[b]	95 % CI[c]
Total	389	343	1481	1137	19.64	12.87	1.53	1.41–1.65
Bacteremia/septicemia	53	39	60	47	0.78	0.51	1.50	1.10–2.08
Septic arthritis	22	2	31	2	0.40	0.02	14.89	6.12–73.7
Osteomyelitis	11	1	13	1	0.17	0.01	10.63	3.39–126.8
Pneumonia	179	135	311	218	4.02	2.39	1.68	1.46–1.95
Lower respiratory tract	52	35	83	52	1.07	0.57	1.88	1.41–2.53
Urinary tract infections	234	224	658	662	8.72	7.49	1.16	1.05–1.30
Urosepsis/pyelonephritis	28	29	38	40	0.49	0.44	1.12	0.77–1.63
Skin/soft tissue	132	59	231	83	2.99	0.91	3.28	2.67–4.07
Gastroenteritis	8	7	10	8	0.13	0.09	1.46	0.68–3.28
Intra-abdominal	17	7	17	7	0.22	0.08	2.76	1.39–6.22
Other	23	15	29	17	0.38	0.19	1.99	1.22–3.36

Curr Rheumatol Rep (2016) 18: 61

Opportunistische Infekte unter Biologika

Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases (level of evidence I–V)

Evidence level	BACTERIA	VIRUS
I	• Tuberculosis	- - -
II	• Salmonellosis (invasive disease) • Legionellosis • Listeria monocytogenes (invasive disease) • Nocardiosis • NTM	• Herpes zoster (any form)
IV	• Cryptosporidium, Microsporidiosis	• Herpes simplex (invasive disease) • HBV reactivation • PML
V	• Bartonellosis (disseminated disease) • Campylobacteriosis (invasive disease) • Shigellosis (invasive disease) • Vibriosis (invasive disease due to V. vulnificus)	• BK virus disease including PVAN • CMV disease • PTLD (EBV) • HCV progression

Winthrop KL, et al. Ann Rheum Dis 2015;74:2107–2116

Opportunistische Infekte unter Biologika

Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases (level of evidence I–V)

Evidence level	FUNGI	PARASITE
I	• - - -	• - - -
II	• Pneumocystis jirovecii • Candidiasis (invasive disease or pharyngeal), Aspergillosis (invasive disease), Mucormycosis, Fusarium, Scedosporium, Pseudallescheria, • Coccidioidomycosis, Histoplasmosis, Cryptococcosis	• - - -
IV	• Blastomycosis	• Visceral Leishmaniasis, Toxoplasmosis, Strongyloides (hyperinfection syndrome)
V	• Paracoccidioides, Penicillium marneffei, Sporothrix schenckii	• Trypanosoma cruzi infection (Chagas' disease)

Winthrop KL, et al. Ann Rheum Dis 2015;74:2107–2116

OPEN ACCESS

EXTENDED REPORT

Evaluation of the RABBIT Risk Score for serious infections

A Zink,[1,2] B Manger,[3] J Kaufmann,[4] C Eisterhues,[5] A Krause,[6] J Listing,[1] A Strangfeld[1]

Table 1 Calculation of the RABBIT Risk Score

Risk factors		V.1: Number of serious infections per 100 PYs	V.2: Percentage of patients with at least one infection per year
Intercept	Always add	−3.996	−4.191
Age	If age >60 add	0.479	0.470
Function (FFbH)	Add	−0.01014*FFbH	−0.00865*FFbH
Alternatively: HAQ	Add	0.362(HAQ-3.16)	0.309(HAQ-3.16)
Chronic lung disease	If yes add	0.522	0.484
Chronic renal disease	If yes add	0.441	0.415
Previous serious infection	If yes add	0.748	0.992
Number of treatment failures	If >5 add	0.443	0.397
Mean glucocorticoid dose	If 7.5–14 mg/day add	0.756	0.782
Mean glucocorticoid dose	If ≥ 15 mg/day add	1.554	1.355
Treatment with TNF inhibitor	If yes (last 3 months) add	0.593	0.589
Calculate the sum of the corresponding values		Sum1	Sum2
Rabbit Risk Score	Calculate	$100*e^{sum1}$	$100*(1-e^{-e^{sum2}})$

FFbH, Hannover Functional Status Questionnaire, Funktionsfragebogen Hannover; HAQ, Health Assessment Questionnaire; PY, patient-years; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy; TNF, tumour necrosis factor.

TBC bei rheumatologischen Erkrankungen

csDMARD erhöhen das TB-Risiko

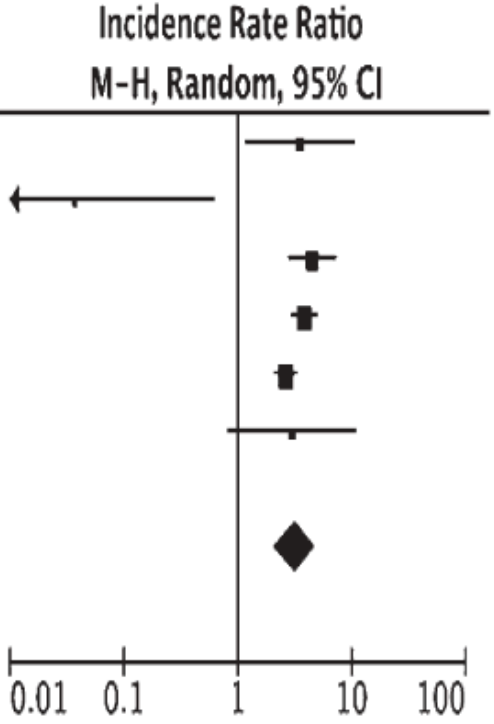
The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with TNF-a Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

Non biological DMARDs: IRR bzgl. TBC von 3,17

	RA/ Non biologic DMARDs		General Population			Incidence Rate Ratio
Study or Subgroup	Events	Pys	Events	Pys	Weight	M-H, Random, 95% CI
Arkema et al. (24)	14	100000	4	100000	9.4%	3.50 [1.15, 10.63]
Dixon et al. (18)	0	100000	13	100000	1.9%	0.04 [0.00, 0.62]
Gomez-Reino et al. (17)	90	100000	20	100000	22.5%	4.50 [2.77, 7.30]
Seong et al. (16)	257	100000	67	100000	29.1%	3.84 [2.93, 5.02]
Tam et al. (20)	242	100000	92	100000	29.9%	2.63 [2.07, 3.34]
Winthrop et al. (21)	9	100000	3	100000	7.3%	3.00 [0.81, 11.08]
Total (95% CI)		**600000**		**600000**	**100.0%**	**3.17 [2.12, 4.73]**
Total events	612		199			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 16.09$, df = 5 (P = 0.007); $I^2 = 69\%$

Test for overall effect: Z = 5.64 (P < 0.00001)



J Rheumatol 2015;42;2229-2237

Biologika erhöhen das TB-Risiko

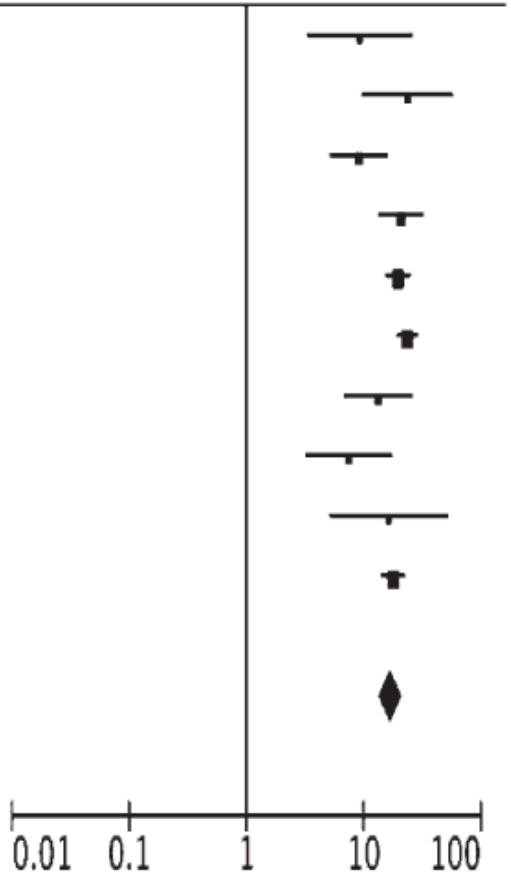
The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with TNF-a Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

Biological DMARDs: IRR bzgl. TBC von 17,7

	RA/Biologic DMARDs		General population			Incidence Rate Ratio
Study or Subgroup	Events	Pys	Events	Pys	Weight	M-H, Random, 95% CI
Arkema et al.(24)	37	100000	4	100000	3.5%	9.25 [3.30, 25.95]
Askling et al.(13)	118	100000	5	100000	4.5%	23.60 [9.64, 57.75]
Dixon et al.(18)	118	100000	13	100000	8.7%	9.08 [5.12, 16.09]
Gomez-Reino et al.(17)	416	100000	20	100000	11.6%	20.80 [13.28, 32.57]
Seong et al.(16)	1316	100000	67	100000	18.5%	19.64 [15.37, 25.10]
Tam et al.(20)	2162	100000	92	100000	19.9%	23.50 [19.08, 28.95]
Tubach et al.(19)	120	100000	9	100000	6.9%	13.33 [6.77, 26.25]
Wallis et al.(14)	45	100000	6	100000	4.8%	7.50 [3.20, 17.58]
Winthrop et al.(21)	49	100000	3	100000	2.8%	16.33 [5.09, 52.40]
Yoo et al.(23)	1299	100000	73	100000	18.8%	17.79 [14.06, 22.52]
Total (95% CI)		**1000000**		**1000000**	**100.0%**	**17.07 [13.85, 21.04]**
Total events	5680		292			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 18.87$, df = 9 (P = 0.03); $I^2 = 52\%$

Test for overall effect: Z = 26.59 (P < 0.00001)



J Rheumatol 2015;42;2229-2237

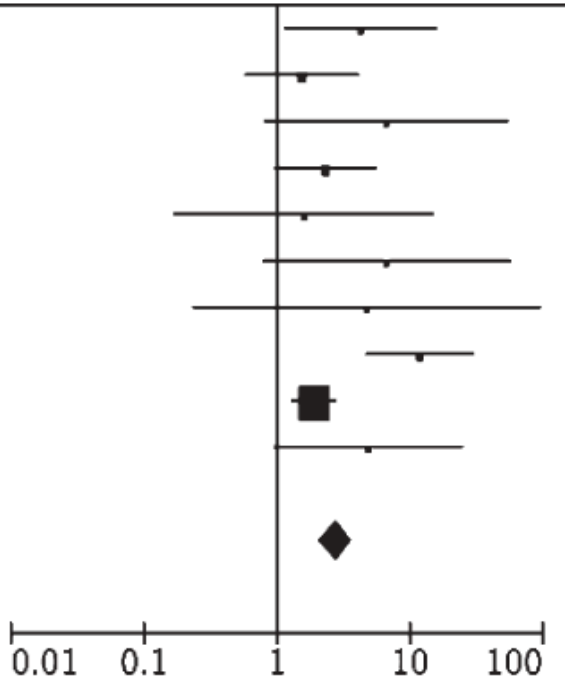
TB-Risiko: Inflix > Eta

The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with TNF-a Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

	Infliximab		Etanercept			Incidence Rate Ratio
Study or Subgroup	Events	Pys	Events	Pys	Weight	M-H, Fixed, 95% CI
Arkema et al.(24)	8	11902	3	19044	3.6%	4.27 [1.13, 16.08]
Askling et al.(13)	11	2050	6	1722	10.1%	1.54 [0.57, 4.16]
Atzeni et al.(22)	6	2320	1	2578	1.5%	6.67 [0.80, 55.34]
Dixon et al.(18)	12	9730	8	15070	9.7%	2.32 [0.95, 5.68]
Favalli et al (25)	3	809	1	429	2.0%	1.59 [0.17, 15.25]
Gomez-Reino et al.(17)	5	1303	1	1740	1.3%	6.68 [0.78, 57.08]
Seong et al. (16)	2	78	0	74	0.8%	4.75 [0.23, 97.26]
Tubach et al.(19)	36	17890	5	29433	5.9%	11.85 [4.65, 30.18]
Wallis et al.(14)	106	196989	32	112994	63.0%	1.90 [1.28, 2.82]
Winthrop et al.(21)	5	6024	2	11765	2.1%	4.88 [0.95, 25.16]
Total (95% CI)		**249095**		**194849**	**100.0%**	**2.78 [2.10, 3.69]**
Total events	194		59			

Heterogeneity: $Chi^2 = 16.82$, df = 9 (P = 0.05); $I^2 = 46\%$

Test for overall effect: Z = 7.14 (P < 0.00001)



J Rheumatol 2015;42;2229-2237

TB-Risiko: Inflix = Ada > Eta

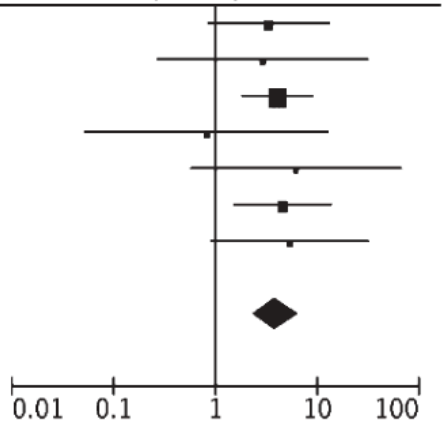
The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with TNF-a Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

TBC Risiko von ADA und INFLIX ist 2,8-3,9x höher als von ETA

Study or Subgroup	Adalimumab Events	Pys	Etanercept Events	Pys	Weight	Incidence Rate Ratio M-H, Fixed, 95% CI
Arkema et al.(24)	6	11447	3	19044	15.9%	3.33 [0.83, 13.30]
Atzeni et al.(22)	2	1772	1	2578	5.7%	2.91 [0.26, 32.06]
Dixon et al.(18)	20	9224	8	15070	42.8%	4.08 [1.80, 9.27]
Favalli et al(25)	1	524	1	429	7.7%	0.82 [0.05, 13.05]
Gomez-Reino et al.(17)	2	565	1	1740	3.5%	6.16 [0.56, 67.80]
Tubach et al.(19)	8	10338	5	29433	18.3%	4.56 [1.49, 13.92]
Winthrop et al.(21)	3	3285	2	11765	6.1%	5.37 [0.90, 32.14]
Total (95% CI)		**37155**		**80059**	**100.0%**	**3.88 [2.31, 6.53]**
Total events	42		21			

Heterogeneity: $Chi^2 = 1.68$, df = 6 (P = 0.95); $I^2 = 0\%$

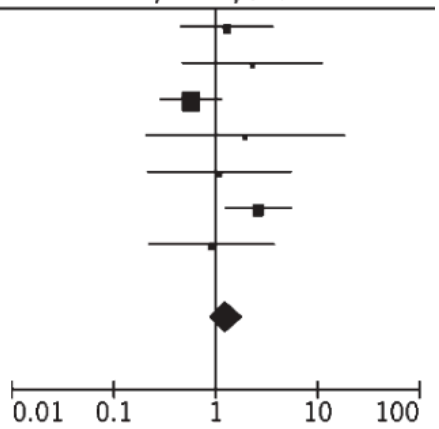
Test for overall effect: Z = 5.10 (P < 0.00001)



Study or Subgroup	Infliximab Events	Pys	Adalimumab Events	Pys	Weight	Incidence Rate Ratio M-H, Fixed, 95% CI
Arkema et al.(24)	8	11902	6	11447	13.0%	1.28 [0.45, 3.69]
Atzeni et al.(22)	6	2320	2	1772	4.8%	2.29 [0.46, 11.34]
Dixon et al.(18)	12	9730	20	9224	43.8%	0.57 [0.28, 1.16]
Favalli et al(25)	3	809	1	524	2.6%	1.94 [0.20, 18.63]
Gomez-Reino et al.(17)	5	1303	2	565	5.9%	1.08 [0.21, 5.57]
Tubach et al.(19)	36	17890	8	10388	21.6%	2.61 [1.22, 5.62]
Winthrop et al.(21)	5	6024	3	3285	8.3%	0.91 [0.22, 3.80]
Total (95% CI)		**49978**		**37205**	**100.0%**	**1.28 [0.87, 1.89]**
Total events	75		42			

Heterogeneity: $Chi^2 = 9.18$, df = 6 (P = 0.16); $I^2 = 35\%$

Test for overall effect: Z = 1.24 (P = 0.21)



J Rheumatol 2015;42;2229-2237

TB-Risiko: Ada > Eta

The risk of tuberculosis disease in rheumatoid arthritis patients on biologics and targeted therapy: A 15-year real world experience in Taiwan

Table 2. Incidence of TB according to bDMARDs and stratified before and after 2012.

	Total	Event (%)	Total person-years	Incidence Rate (/10^5 years)	IRR (95% CI) †
2000–2015					
ETN	443	13 (2.9)	1461.8	889.3	1
ADA	332	11 (3.3)	1042.1	1055.6	1.27 (0.76–2.13)[&]
GLN	60	0 (0.0)	94.0	0	-
TCZ	31	0 (0.0)	55.5	0	-
ABA	74	0 (0.0)	105.3	0	-
TOF	11	0 (0.0)	1.9	0	-
Total	951	24(2.5)	2758.7	870.0	-

Zusammenfassend: TB-Risiko: Inflix = Ada > Eta

TB-Risiko besteht auch bei Tofacitinib = janus kinase (JAK) inhibitor

Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis

Table 2 TB IRs for tofacitinib patients by background country IRs* (phase II, III and LTE studies)

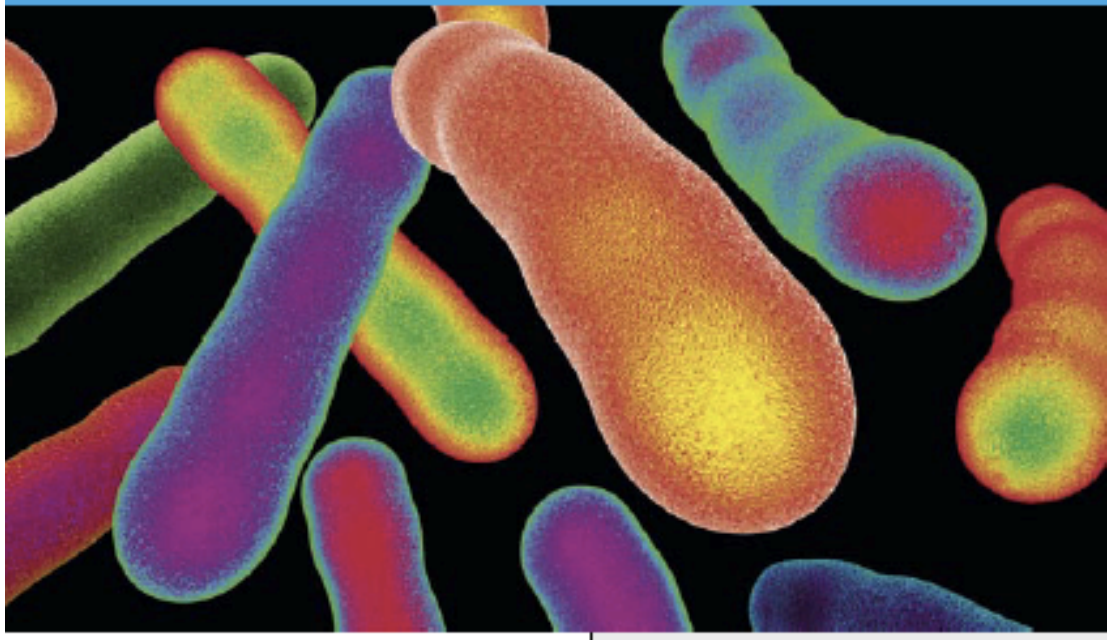
	TB cases with tofacitinib (n)	Tofacitinib exposure (patient-years)	Crude TB IR † (95% CI)
Low‡ (0.01)	1	4852.3	0.02 (0.003 to 0.15)
Medium§ (≥0.01 and ≤0.05)	4	5020.5	0.08 (0.03 to 0.21)
High¶ (>0.05)	21	2791.1	0.75 (0.49 to 1.15)

Winthrop KL, et al. Ann Rheum Dis 2016;75:1133–1138.

Österreichische
ÄrzteZeitung
ÖÄZ
Die Zeitschrift der Ärztinnen und Ärzte

März 2011

Supplementum



Consensus medical dialogue Statement

Tuberkulose & Biologika

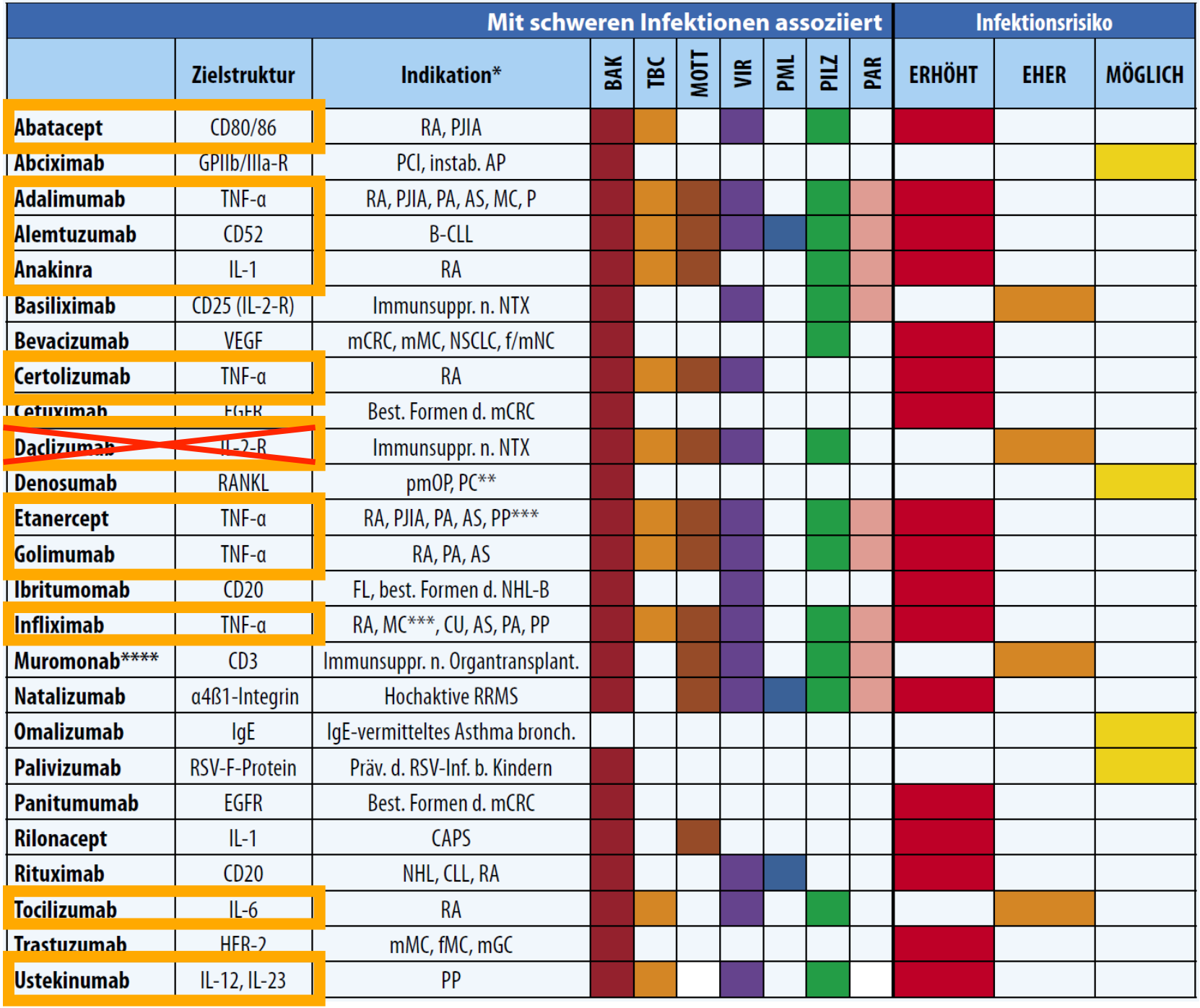
Vorsitz: Prim. Priv.-Doz. Dr. Burkhard Leeb, Univ.-Prof. Dr. Florian Thalhammer **Teilnehmer:** Univ.-Prof. Dr. Hans-Peter Brezinschek, Prim. Univ.-Prof. Dr. Hans Bröll, Prim. Univ.-Doz. Dr. Ludwig Erlacher, Dr. Markus Gaugg, Univ.-Prof. DDr. Manfred Herold, Mag. Dr. Alexander Indra, Prim. Univ.-Prof. Dr. Meinhard Kneussl, Prim. Univ.-Prof. Dr. Peter Knoflach, Univ.-Prof. Dr. Robert Krause, Univ.-Prof. Dr. Gottfried Novacek, Dr. Pavol Papay, Univ.-Prof. Dr. Walter Reinisch, OA Dr. Rudolf Rumetshofer, Prim. Univ.-Prof. Dr. Franz Trautinger, Univ.-Prof. Dr. Günter Weiss, Prim. Univ.-Doz. Dr. Christoph Wenisch, Univ.-Prof. Dr. Stefan Winkler.

Österreichische Gesellschaft für Rheumatologie & Rehabilitation (ÖGR)

ÖGI Österreichische Gesellschaft für Infektionskrankheiten (ÖGI)

Österreichische Gesellschaft für Dermatologie und Venerologie (ÖGDV)

ÖGGH Österreichische Gesellschaft für Gastroenterologie & Hepatologie (ÖGGH)



Leeb B., Thalhammer F. et al. Österreichische Ärztezeitung März 2011

Screening auf latente TBC

Def. der latenten TBC (LTBI)

Definition latente Tuberkulose:

- Z.n. Primärinfektion mit der Folge einer Persistenz vitaler Bakterien im Organismus (dormant persister) ohne Organbefund bzw. ohne Erkrankung.

- Aus einer LTBI kann sich jederzeit (auch Jahrzehnte nach der Primärinfektion) eine aktive TBC entwickeln (Reaktivierung).

Flick H, Rumetshofer R, Wurzinger G. Wien Klin Wochenschr Educ DOI 10.1007/s11812-012-0018-2

Diagnostische Indikatoren (gleichwertig!) für eine LTBI

Vor Einleitung einer Biologika-Therapie sind folgende Kriterien für das Vorliegen einer LTBI zu prüfen:

anamnestische Kriterien	immunologische Kriterien	radiologische Kriterien
• relevante Tbc-Exposition[1] • Herkunft aus Hochende-mieland • unvollständig behandelte aktive Tbc[1]	• positiver IGRA • positiver MMT[2]	• intrapulmonale Rundherde[3] • narbige pleurale Residuen[4] • verkalkte Lymphknoten • Perikardverkalkungen

Ein positives Kriterium ist ausreichend für die Indikation zur Chemoprävention.

Negative IGRA-Ergebnisse allein sind nicht ausreichend, um anamnestische oder radiologische Kriterien zu entkräften.

__1__ in der Vergangenheit; __2__ bei Nicht-BCG-Geimpften; __3__ verkalkt oder nicht verkalkt (sofern nicht alternativ erklärt); __4__ z.B. Pleuraschwarten, Spitzenfibrosen, Pleuraschwielen (sofern nicht alternativ erklärt)

Olschewski H et al. Pneumo 2012

Diagnostische Indikatoren (gleichwertig!) für eine LTBI

Vor Einleitung einer Biologika-Therapie sind folgende Kriterien für das Vorliegen einer LTBI zu prüfen:

anamnestische Kriterien	immunologische Kriterien	radiologische Kriterien
• relevante Tbc-E • Herkunft aus H mieland • unvollständig b aktive Tbc[1]		e Rundherde[3] e Residuen[4] hknoten ungen

Aber merke:
Für die Diagnose einer *LTBI gibt es keinen Goldstandard*

Ein positives Kri … oprävention.

Negative IGRA-Ergebnisse allein sind nicht ausreichend, um anamnestische oder radiologische Kriterien zu entkräften.

1 in der Vergangenheit; 2 bei Nicht-BCG-Geimpften; 3 verkalkt oder nicht verkalkt (sofern nicht alternativ erklärt); 4 z.B. Pleuraschwarten, Spitzenfibrosen, Pleuraschwielen (sofern nicht alternativ erklärt)

Olschewski H et al. Pneumo 2012

Homepage der DGR (2017)

http://www.dgrh.de/tnfblockertbc.html

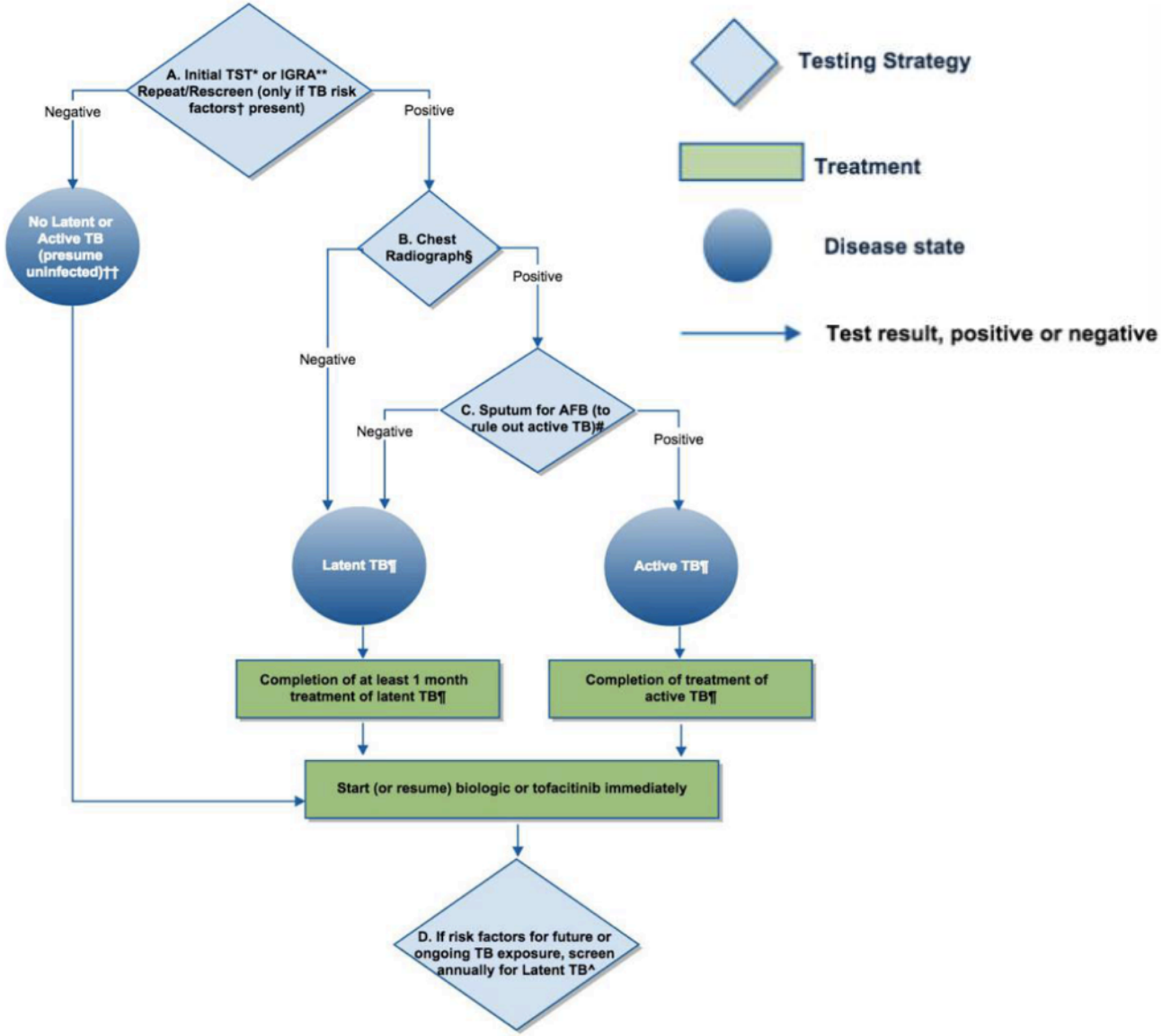
Homepage der DGR (2017)

Tabelle: Vorgehensweise zum Screening auf latente tuberkulöse Infektion (LTBI) von Patienten mit rheumatoider Arthritis vor Anti-TNF-α-Therapie

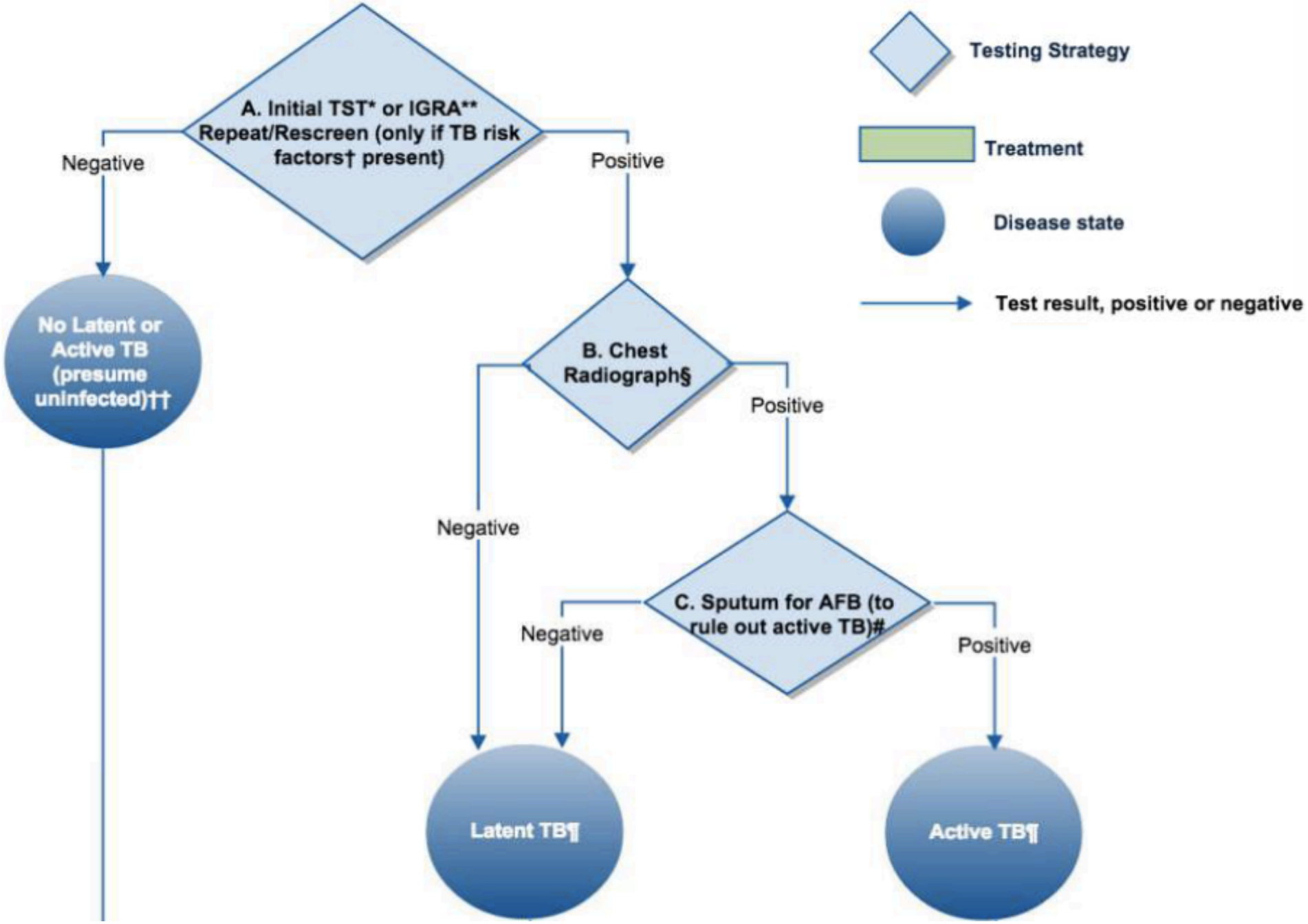
Anamnese: Immunsuppression, andere Risikofaktoren für Tuberkulose, frühere LTBI/TB, (berufliche) TB-Kontakte, Herkunft, BCG-Impfstatus, THT/IGRA-Status, Vergleichs-Thoraxröntgenaufnahmen
Ausschluss einer behandlungsbedürftigen Lungen-TB: klinische Untersuchung, IGRA, Röntgenthorax in 2 Ebenen, ggf. Thorax-Computertomografie, ggf. bakteriologische Untersuchung → falls IGRA negativ, erübrigt sich in der Regel Chemoprävention → falls IGRA positiv, nach Ausschluss einer behandlungsbedürftigen TB → chemopräventive Therapie (s. unten)
bei röntgenologischen Zeichen einer durchgemachten, aber un- bzw. unzureichend behandelten TB ohne Anhalt für Aktivität (kalzifizierte Knötchen, Spitzenfibrose, Pleuraschwielen), unabhängig vom Ergebnis eines IGRA-Tests → chemopräventive Therapie
ergänzender THT nur sinnvoll, falls: → trotz eines negativen IGRA-Tests frühere enge Exposition gegenüber einem Patienten mit infektiöser Lungen-TB anamnestisch plausibel ist → eine BCG-Impfung unter Berücksichtigung der Impfpolitik im jeweiligen Herkunftsland des Patienten unwahrscheinlich ist und/oder → ein IGRA-Test auch in der Wiederholung unbestimmbar ist In diesen Fällen bestimmt ein positiver THT das weitere Vorgehen.
In jedem Fall: → umfassende Aufklärung der Patienten über erhöhtes TB-Risiko unter Anti-TNF-α-Therapie sowie über mögliche Symptome und Notwendigkeit umgehender ärztlicher Abklärung → unter Anti-TNF-α-Therapie (auch unter bzw. nach Chemoprävention) regelmäßige Abfrage TB-typischer Symptome und ggf. Veranlassung weiterführender Untersuchungen

http://www.dgrh.de/tnfblockertbc.html

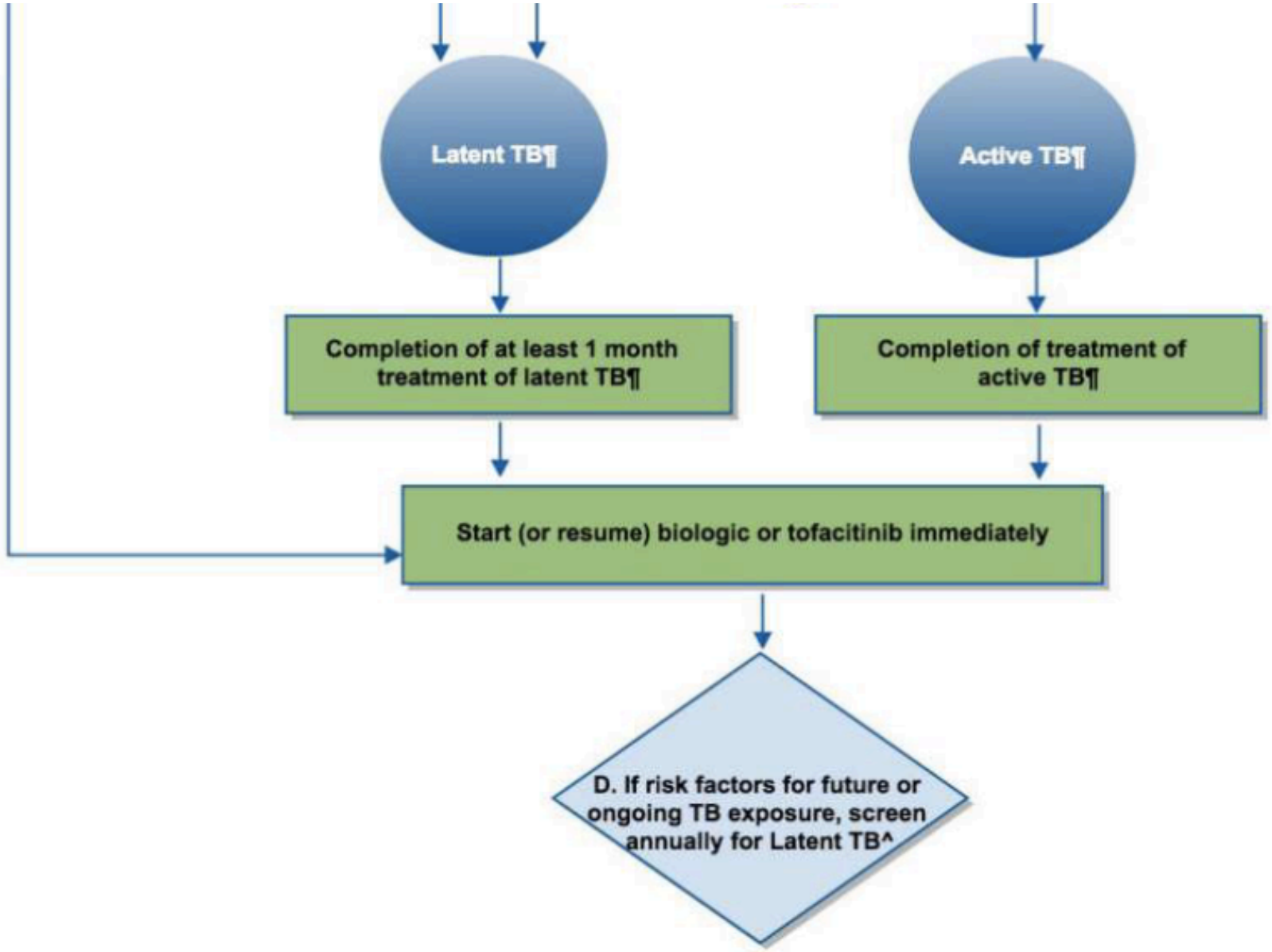
2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis



Arthritis Care & Research, DOI 10.1002/acr.22783, VC 2015, American College of Rheumatology



Arthritis Care & Research, DOI 10.1002/acr.22783, VC 2015, American College of Rheumatology



Arthritis Care & Research, DOI 10.1002/acr.22783, VC 2015, American College of Rheumatology

THT oder IGRA?

Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis

Table 1 Characteristics of included studies

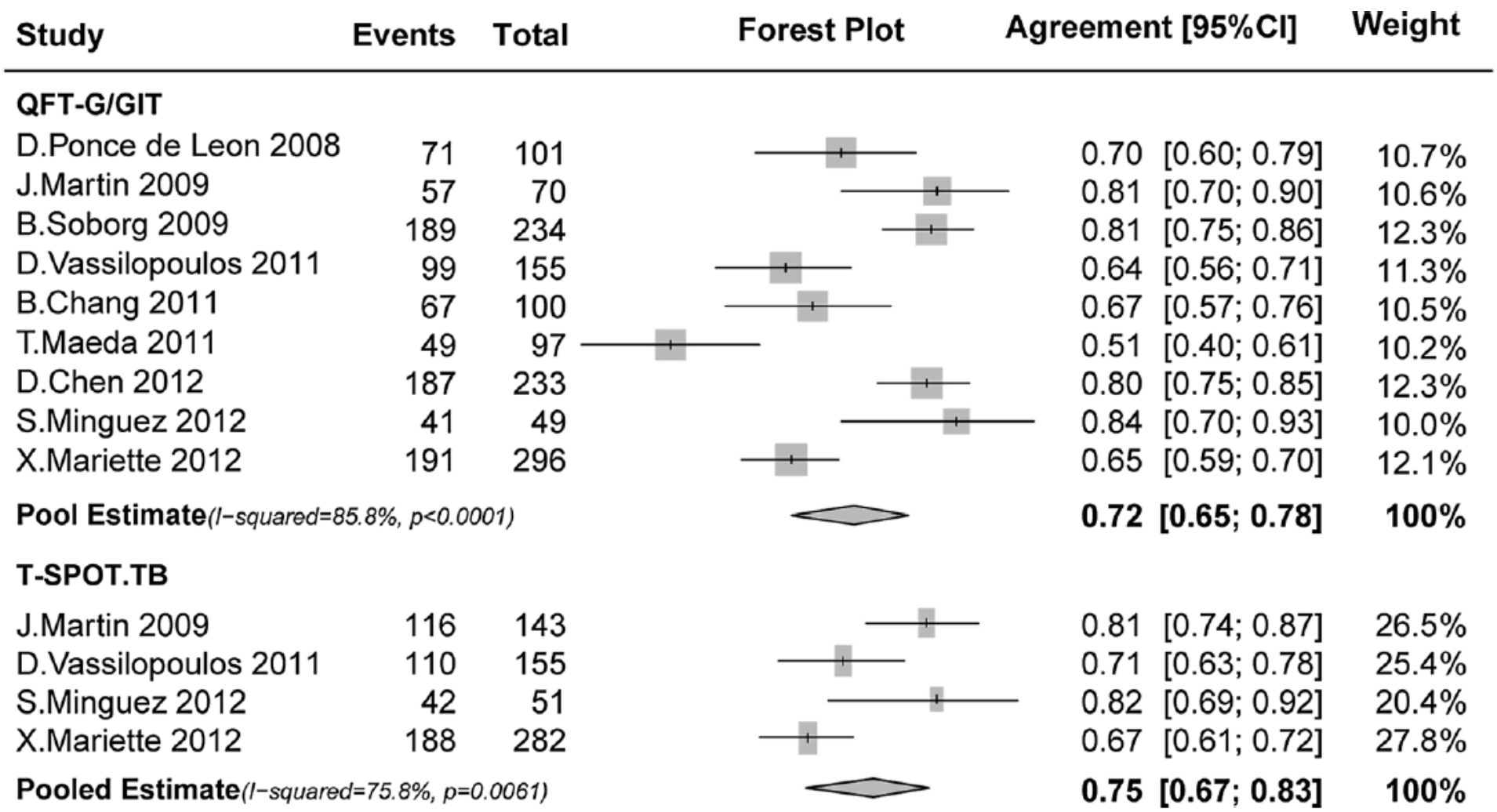
First author [ref.]	Country	Individuals assessed	Type of rheumatic disease	Mean age (year)	Female (%)	BCG vaccinated (%)	IGRA used	TST cut-off (mm)
D. Ponce de Leon 2008 [23]	Peru	106	RA	57.6±12.6	90.1	80.2	QFT-GIT	≥5 mm
B. Soborg 2009 [24]	Denmark	302	RA, spondyloarthropathies, sarcoidosis, and others	49.8 (median)	62	At least 50	QFT-G	>12 mm (BCG vaccinated) and >6 mm (BCG unvaccinated)
J. Martin 2010 [25]	Ireland	150	RA, PsA, JIA, and others	50.1±11.6	60.7	At least 82	QFT-G T-SPOT.TB	>5 mm
D. Vassilopoulos 2011 [26]	Greece	157	RA, PsA, AS, and other spondyloarthropathies	52±16	58.1	76	QFT-GIT T-SPOT.TB	≥5 mm
B. Chang 2011 [27]	South Korea	107	RA and AS	39 (median)	41.1	59	QFT-GIT	≥10 mm
E. Belard 2011 [28]	Denmark	248	RA andspondyloarthropathies	47 (media)	66.5	At least 62	QFT-GIT	>10 mm (BCG vaccinated) And >5 mm (BCG unvaccinated)
T. Maeda 2011 [29]	Japan	97	RA	61.9±10.4	76.3	Almost all	QFT-G	≥10 mm
D. Chen 2012 [30]	Taiwan	242	RA	54.7	82.4	97.9	QFT-G	≥5 mm
S. Minguez 2012 [31]	Spain	53	RA, AS, PsA, and others	49.6±13.0	66.0	5.7[b]	QFT-GIT T-SPOT.TB	>5 mm
X. Mariette 2012 [32]	France	301	RA and SpA	47.4±14.1	60.1	65.1	QFT-GIT T-SPOT.TB	≥5 mm
M. Klein 2013 [33]	Czech Republic	177	RA, AS, PsA and JIA	44.2±14.8	–	–	QFT-GIT	≥5 mm

Clin Rheumatol (2016) 35:417–425

THT und IGRAs stimmen nur in 70% der Fälle überein

Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis

Fig. 1 Agreement between IGRAs and TST

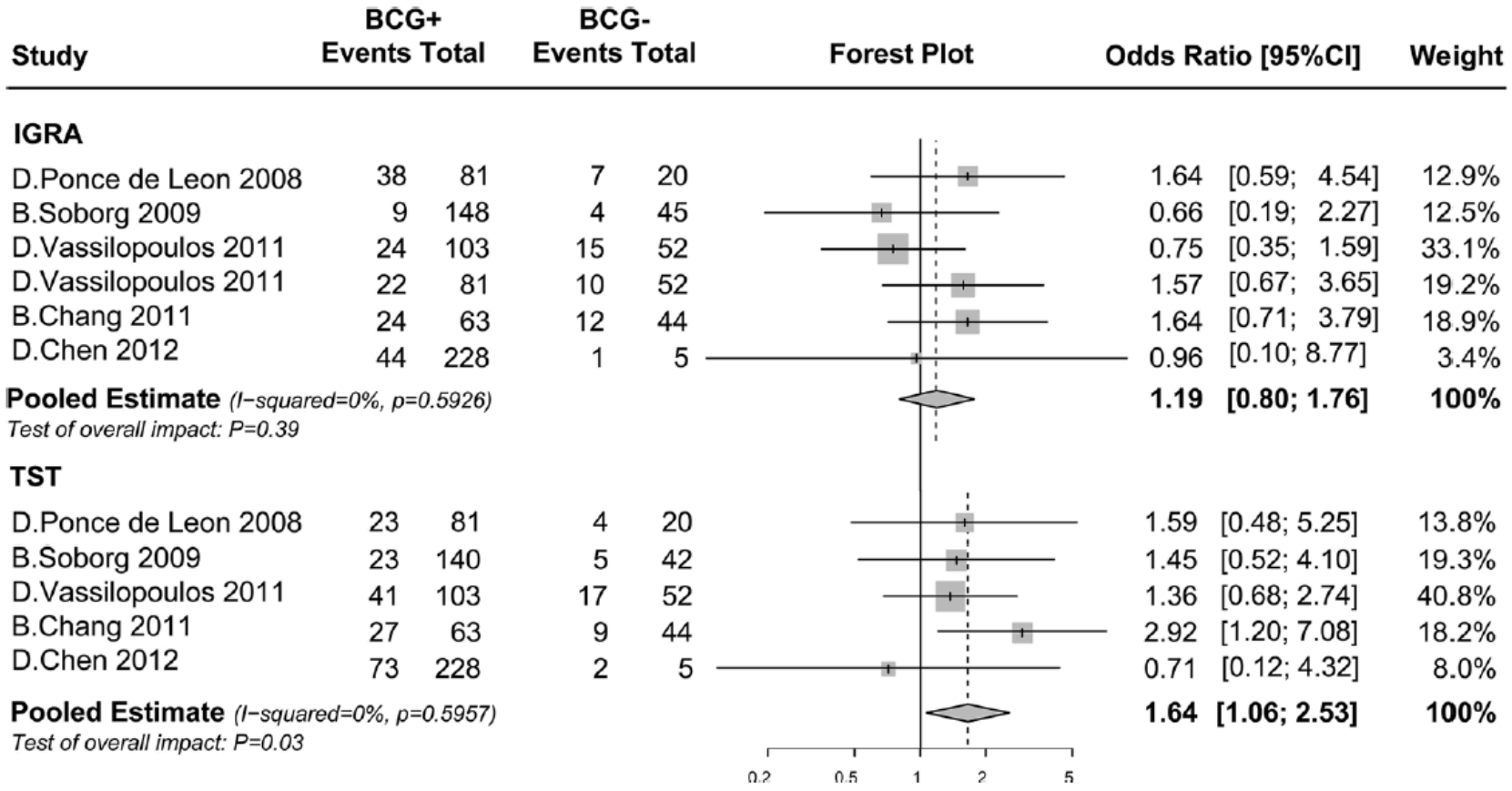


Clin Rheumatol (2016) 35:417–425

THT und IGRAs stimmen nur in 70% der Fälle überein (Hauptproblem: BCG-Impfung)

Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis

Fig. 2 BCG vaccination status and test results of IGRAs and TST

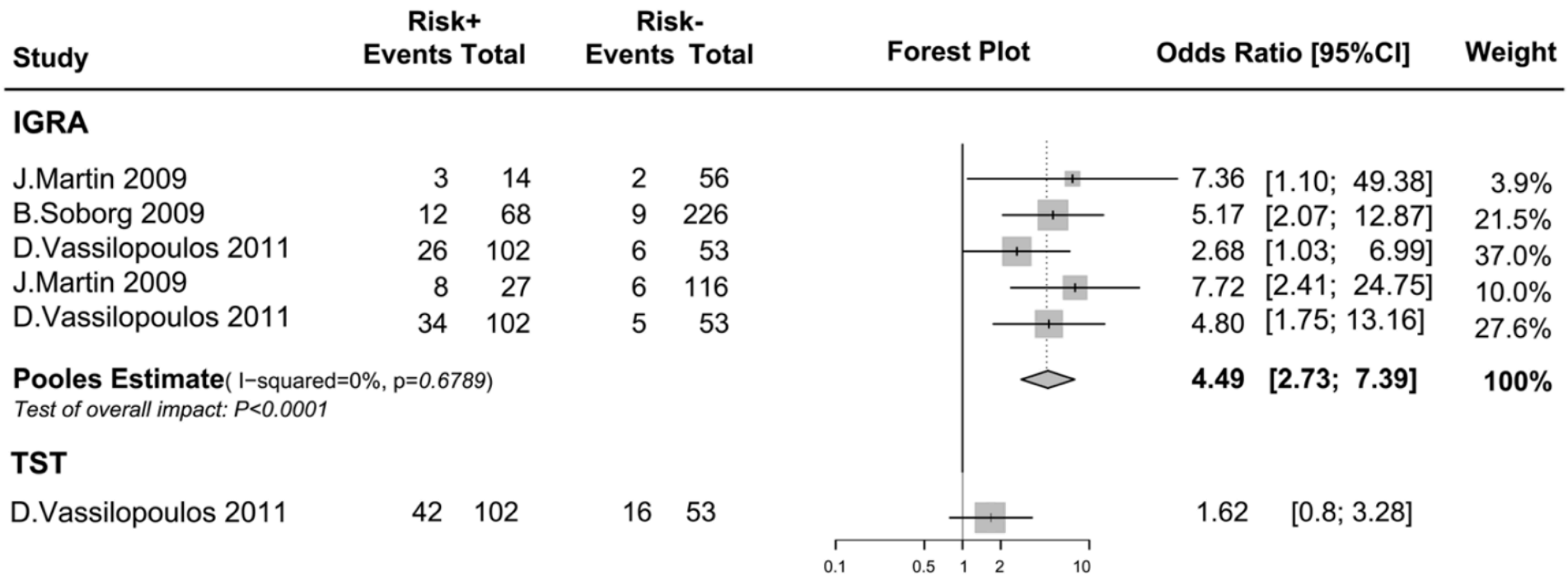


Clin Rheumatol (2016) 35:417–425

IGRAs spiegeln das TBC Risiko besser wieder

Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis

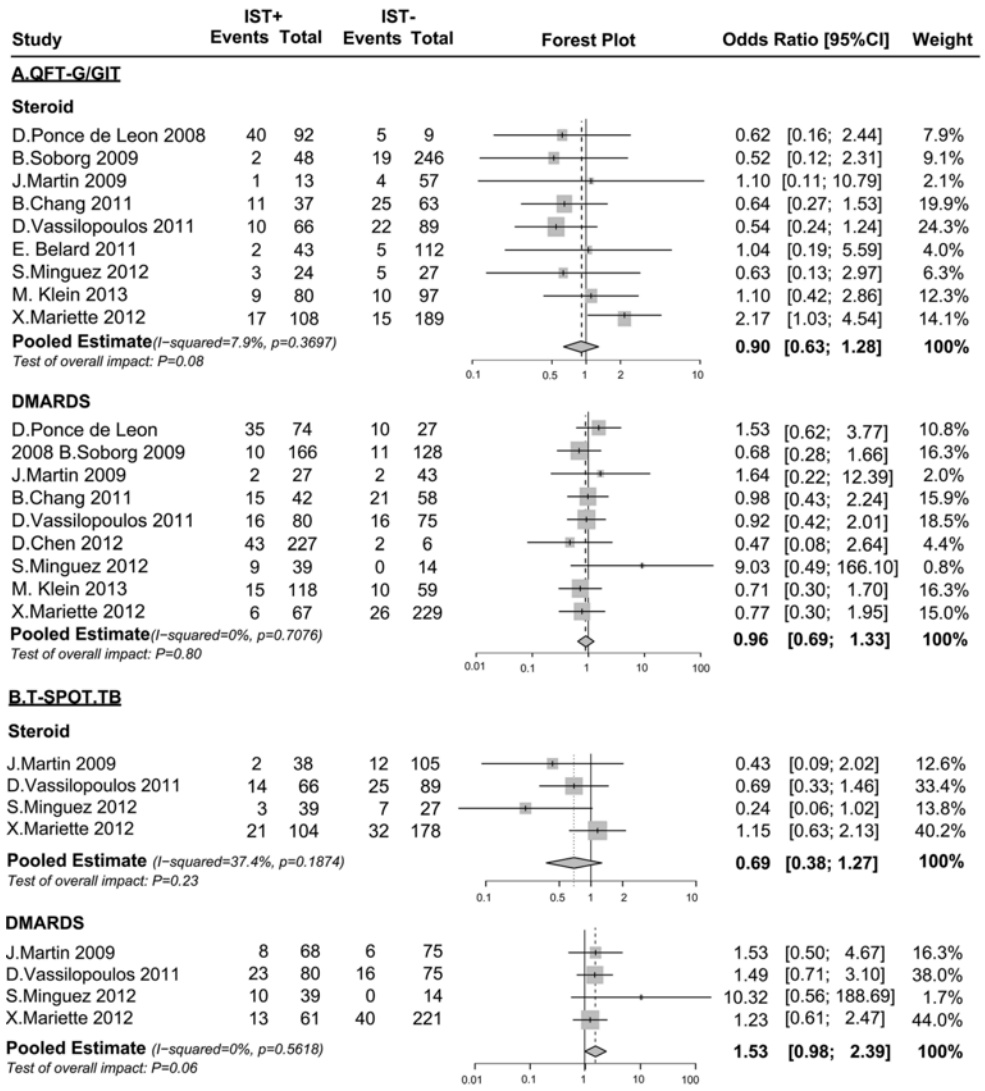
Fig. 3 Tuberculosis risk and test results of IGRAs and TST



Clin Rheumatol (2016) 35:417–425

IGRAs werden durch Immunsuppressiva nicht wesentlich beeinflusst

Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis

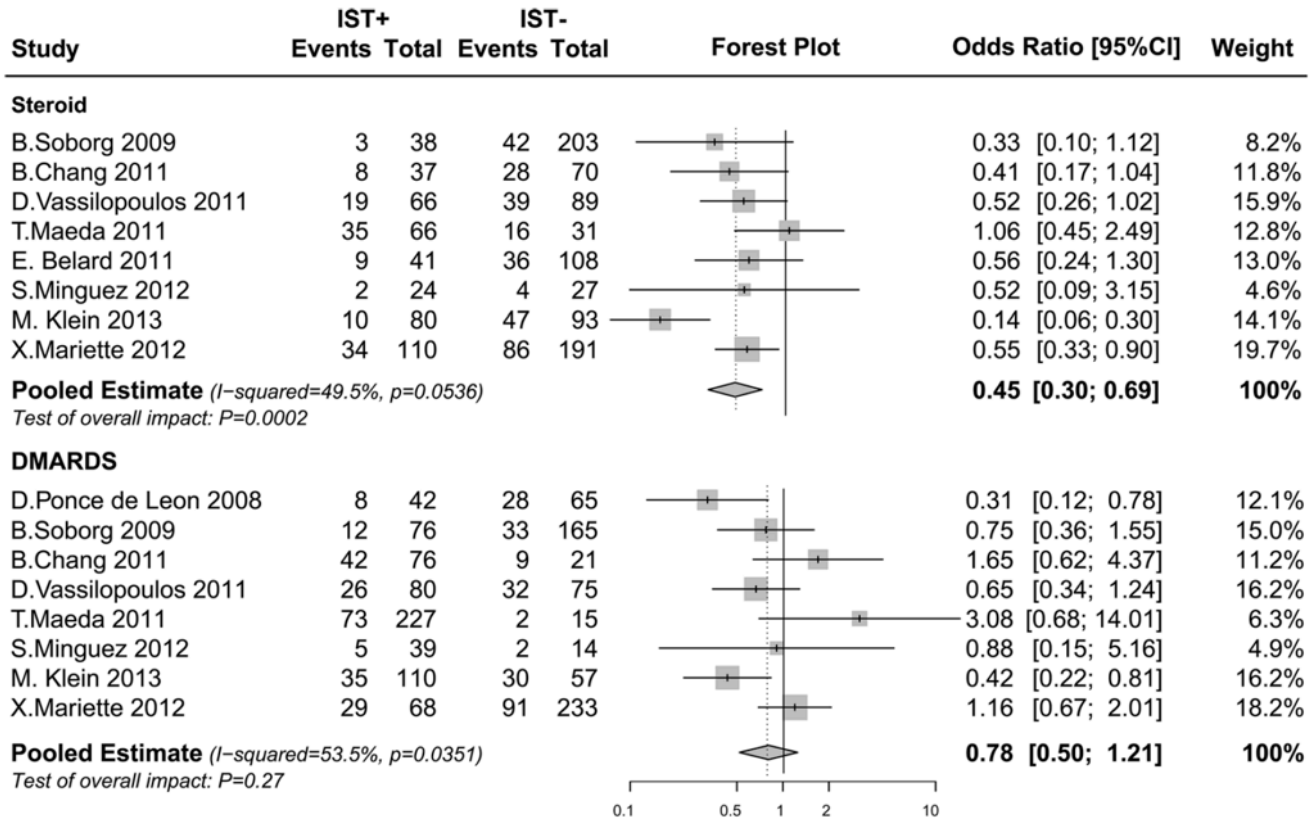


Clin Rheumatol (2016) 35:417–425

THTs werden vor allem durch Steroid beeinflusst

Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis

Fig. 5 Impact of immunosuppressive therapy on TST results. *IST* immunosuppressive therapy, *DMARDs* disease-modifying anti-rheumatic drugs



Clin Rheumatol (2016) 35:417–425

Sollten neg. IGRAs unter laufender Biologika-Therapie jährlich kontrolliert werden?

The conversion rate of tuberculosis screening tests during biological therapies in patients with rheumatoid arthritis

Ca. 14% im Verlauf „Serokonversion“ (IGRA neg. → pos.)

Characteristic	Total ($n = 249$)	Converters ($n = 34$)	Non-converters ($n = 215$)	p value
Sex (M/F)	39/210	11/23	28/187	0.0089
Age (years), mean ± SD	54.3 ± 11.9	59 ± 8.7	53.6 ± 12.3	0.017

... aber keiner entwickelte eine TBC.

Empfehlung (H. Flick):
IGRA „Kontrolle“ nur bei Pat. mit frischer TBC Exposition (z.B. nach Urlaubsreise in TBC-Hochendemieland!)

Clin Rheumatol (2017) 36:457–461

LTBI Chemoprophylaxe vor TNFa ist effektiv

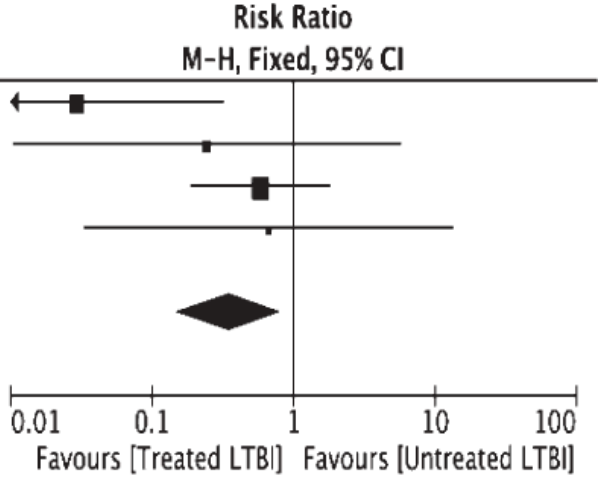
The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with TNF-a Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

TBC Risiko: wird durch INH Behandlung bei LTBI effektiv reduziert

Study or Subgroup	Treated LTBI Events	Total	Untreated LTBI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gomez-Reino et al.2007 (17)	1	1154	2	68	33.9%	0.03 [0.00, 0.32]
Seong et al.2007 (16)	0	36	1	26	15.6%	0.24 [0.01, 5.74]
Sichletidis et al.2006 (15)	7	36	3	9	43.1%	0.58 [0.19, 1.82]
Tam et al.2013 (20)	1	17	0	3	7.4%	0.67 [0.03, 13.55]
Total (95% CI)		**1243**		**106**	**100.0%**	**0.35 [0.15, 0.82]**
Total events	9		6			

Heterogeneity: $Chi^2 = 5.13$, df = 3 (P = 0.16); $I^2 = 41\%$

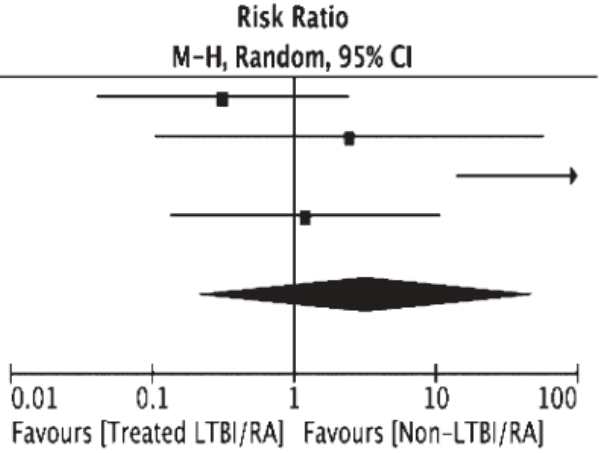
Test for overall effect: Z = 2.43 (P = 0.02)



Study or Subgroup	Treated LTBI/RA Events	Total	Non-LTBI/RA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gomez-Reino et al.2007 (17)	1	1154	11	3976	26.3%	0.31 [0.04, 2.42]
Seong et al.2007 (16)	0	17	1	131	21.9%	2.44 [0.10, 57.76]
Sichletidis et al.2006 (15)	7	36	1	568	26.2%	110.44 [13.96, 873.53]
Tam et al.2013 (20)	1	17	3	61	25.7%	1.20 [0.13, 10.78]
Total (95% CI)		**1224**		**4736**	**100.0%**	**3.22 [0.20, 51.37]**
Total events	9		16			

Heterogeneity: $Tau^2 = 6.52$; $Chi^2 = 17.25$, df = 3 (P = 0.0006); $I^2 = 83\%$

Test for overall effect: Z = 0.83 (P = 0.41)



J Rheumatol 2015;42;2229-2237

TBC kann trotz LTBI Chemoprophylaxe auftreten (vor allem in Hochendemieländern durch Neuinfektion)

The risk of tuberculosis disease in rheumatoid arthritis patients on biologics and targeted therapy: A 15-year real world experience in Taiwan

Table 2. Incidence of TB according to bDMARDs and stratified before and after 2012.

	Total	Event (%)	Total person-years	Incidence Rate (/10^5 years)	IRR (95% CI) †
2000–2011					
ETN	335	10 (3.0)	1286.4	777.4	1
ADA	236	9 (3.8)	906.0	993.4	1.35 (0.73–2.48)*
GLN	-	-	-	-	-
TCZ	-	-	-	-	-
ABA	-	-	-	-	-
TOF	-	-	-	-	-
Total	571	19(3.3)	2192.4	866.6	-
2012–2015					
ETN	108	3 (2.8)	175.4	1710.6	1
ADA	96	2(2.1)	136.1	1469.1	1.09 (0.55–2.19)#
GLN	60	0 (0.0)	94	0.0	-
TCZ	31	0 (0.0)	55.49	0.0	-
ABA	74	0 (0.0)	105.3	0.0	-
TOF	11	0 (0.0)	1.91	0.0	-
Total	380	5(1.3)	568.2	879.9	-

2012 wurde in Taiwan mit LTBI Screening begonnen

PLOS ONE | https://doi.org/10.1371/journal.pone.0178035 June 1, 2017

Medikament	Prinzip	Leeb Österreich 2011	Mok Hong Kong 2011 (RA)	De Keyser Belgien 2011 (RA)	Sivamani USA 2012 (Psor.)	Rote Liste 2012
Abatacept **ORENCIA®** **RA** (Psoriasis)	CD80, CD86	**IGRA**	**IGRA**	**IGRA**	**IGRA**	**IGRA**
Anakinra **KINERET®** **RA**	IL-1	**IGRA**	-	-	-	Mykobakt. Infektionen als NW benannt
Tocilizumab **RoActemra®** **RA**	IL-6	**IGRA**	-	**IGRA**	-	**IGRA**
Ustekinumab **STELARA®** **Psoriasis**	IL-12, IL-23	**IGRA**	-	-	**IGRA**	**IGRA**
Alemtuzumab **MabCampath®** **B-CLL**	CD52	**IGRA**	-	-	-	TBC als NW benannt

Leeb B., Thalhammer F. et al. Österreichische Ärztezeitung März 2011
Holle et al. Z Rheumatol 2008 · 67:295–304
De Keyser. Current Rheumatology Reviews, 2011, 7, 77-87
Mok et al. Clin Rheumatol (2011) 30:303–312
Sivamani et al. Clinic Rev Allerg Immunol, online 05th feb. 2012

Chemoprophylaxe bei LTBI

Infektion, LTBI, Primär- und Postprimärtuberkulose

(Unterschied zwischen Chemoprophylaxe und –prävention)

Chemoprophylaxe (griech. Vorbeugung)

Chemoprävention (lat. Zuvorkommen)

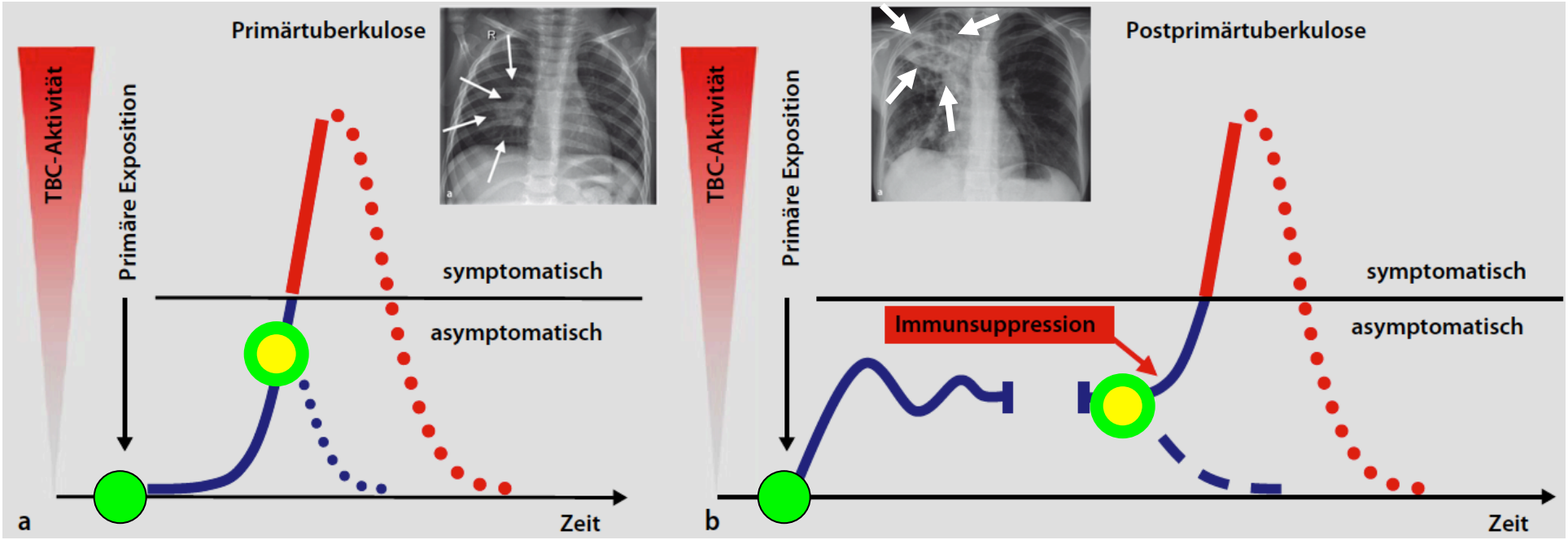
Latente Infektion (LTBI)

Chemoprävention nach rezenter Exposition

Chemoprävention vor Immunsuppression

Aktive Tuberkulose

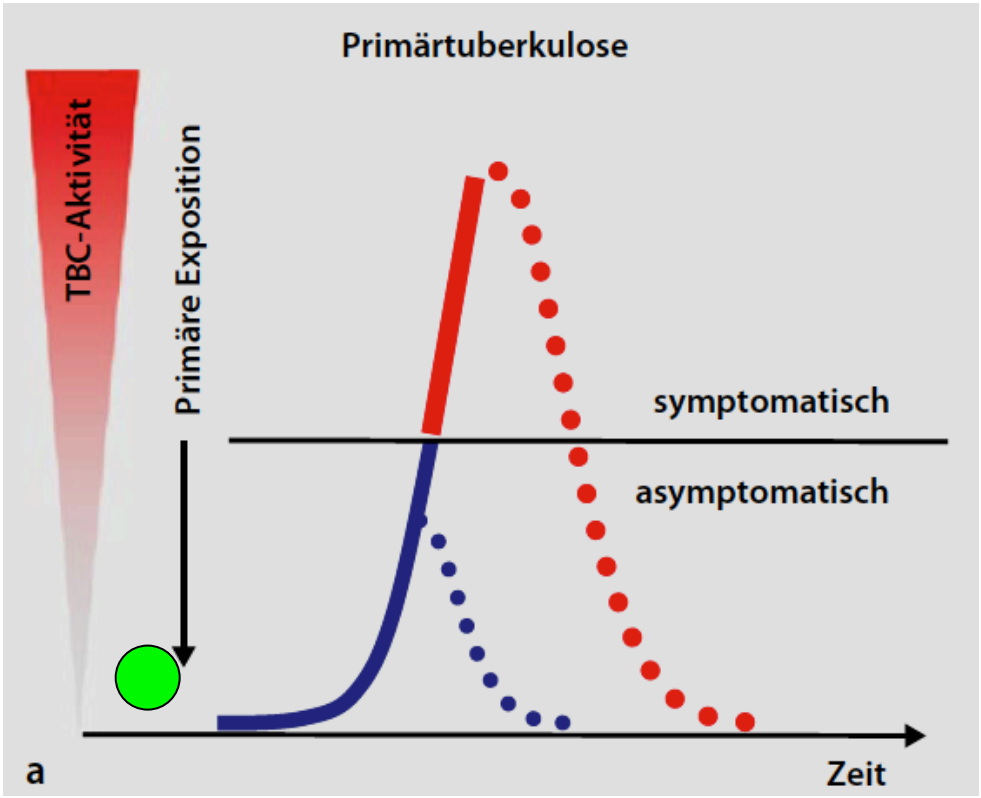
Kombinationstherapie bei aktiver TBC



Adaptiert nach Flick H. und Wurzinger G. Lungentuberkulose. Der Pneumologe 4 · 2013

Chemoprophylaxe direkt nach „frischer“ Exposition

Chemoprophylaxe (griech. Vorbeugung)



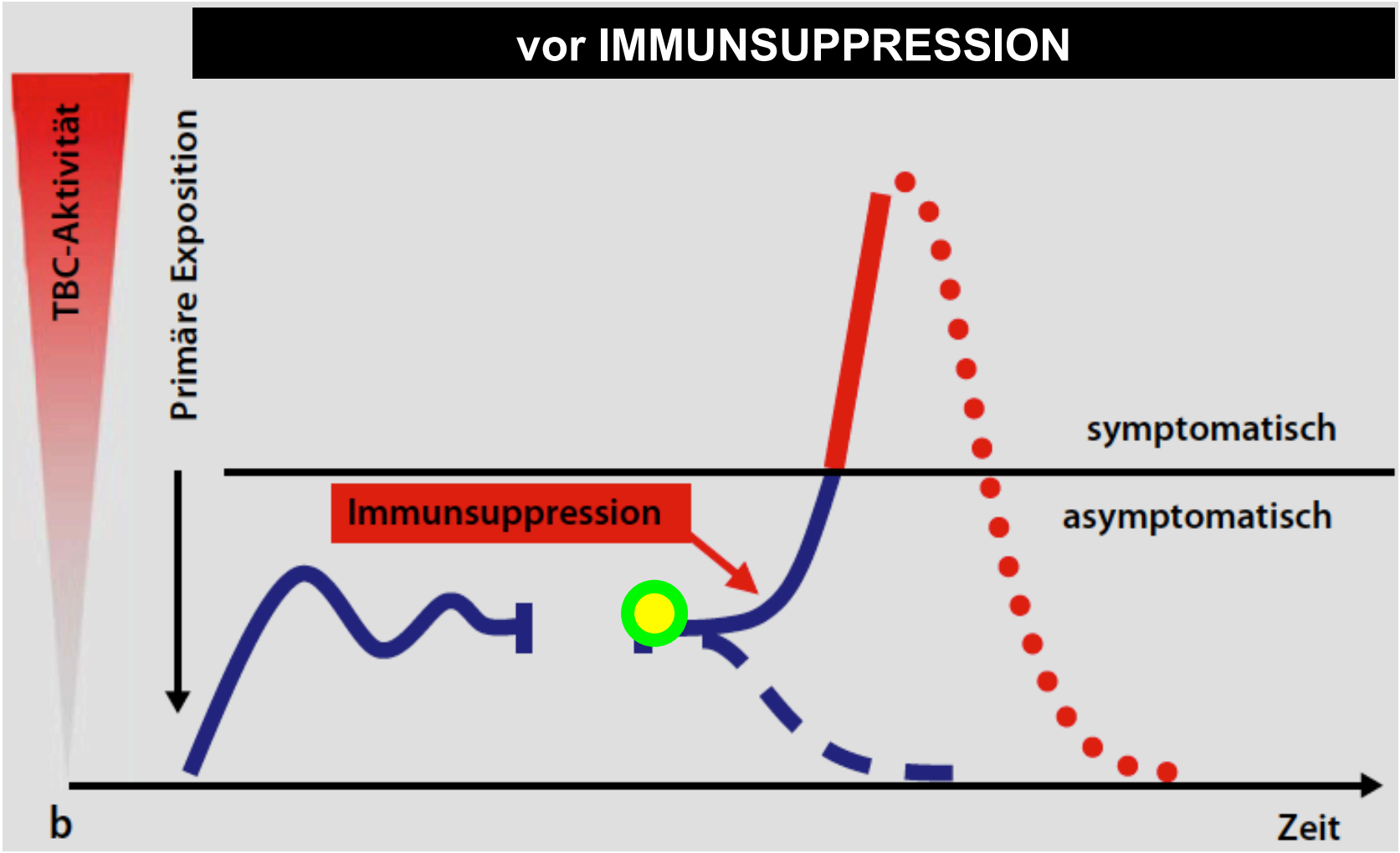
Chemoprophylaxe

=

Postexpositionsprophylaxe noch vor Vorliegen eines endgültigen Befundes über die erfolgte Ansteckung

Adaptiert nach Flick H. und Wurzinger G. Lungentuberkulose. Der Pneumologe 4 · 2013

Chemoprävention vor Immunsuppression



Adaptiert nach Flick H. und Wurzinger G. Lungentuberkulose. Der Pneumologe 4 · 2013

TBC-Chemoprävention vor Biologika

Therapie der 1. Wahl	Dosis	Dauer
Isoniazid	5 mg/kg KG/d (max. 300 mg/d)	9 Monate

Therapie der 2. Wahl	Dosis	Dauer
Isoniazid	5 mg/kg KG/d (max. 300 mg/d)	6 Monate
Rifampicin	10 mg/kg KG/d (max. 600mg/d)	4 Monate

Adapted from:
1. Blumberg HM, Leonard MK Jr, Jasmer RM. Update on treatment of tuberculosis and latent tuberculosis infection. JAMA 2005; 293:2776.
2. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011; 60(48):1650.

TBC-Chemoprävention (Vorgehen)

Vor Beginn der präventiven Therapie:

- Aktive TBC sicher ausschließen und Indikation für Chemoprävention prüfen
- Risikofaktoren für Komplikationen prüfen
- Patient über Risiken aufklären (schriftliches Einverständnis)
- Bestimmung Leberenzyme, Kreatinin, Blutbild

Erste Kontrolle 14 Tage nach Beginn der präventiven Therapie

- Allgemeine Verträglichkeit
- Bestimmung Leberenzyme

Dann Kontrollen aller 4 Wochen

- Allgemeine Verträglichkeit
- Bestimmung Leberenzyme

Nach Abschluss der präventiven Therapie

- Röntgen-Thorax (zum Ausschluss einer MDR)

Flick H, Rumetshofer R, Wurzinger G. Wien Klin Wochenschr Educ DOI 10.1007/s11812-012-0018-2

INH-Toxizität (relevante Faktoren)

INH-Toxizität wird beeinflusst von folgenden Faktoren:

- Alter
- Alkoholkonsum
- CYP (P450) Interaktionen
- Hepatoxische Medikamente
- Neuropathy-Risikofaktoren (Diabetes und Alkoholabhängigkeit)
- IVDA
- Schwangerschaft und postpartale Periode
- Frauen (vor allem „non-white“)
- (chronische Hepatitis)

Aminoglutethimide
Armodafinil*
Bexarotene*
Bosentan
Carbamazepine
Deferasirox*
Dexamethasone
Efavirenz
Enzalutamide
Etravirine
Fosphenytoin
Griseofulvin*
Mitotane*
Modafinil*
Nafcillin
Nevirapine
Oxcarbazepine
Pentobarbital
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin (rifampicin)
Rifapentine
Rufinamide*
St. John's wort*
Vemurafenib*

Kunst H et al. INT J TUBERC LUNG DIS 14(11):1374–1381

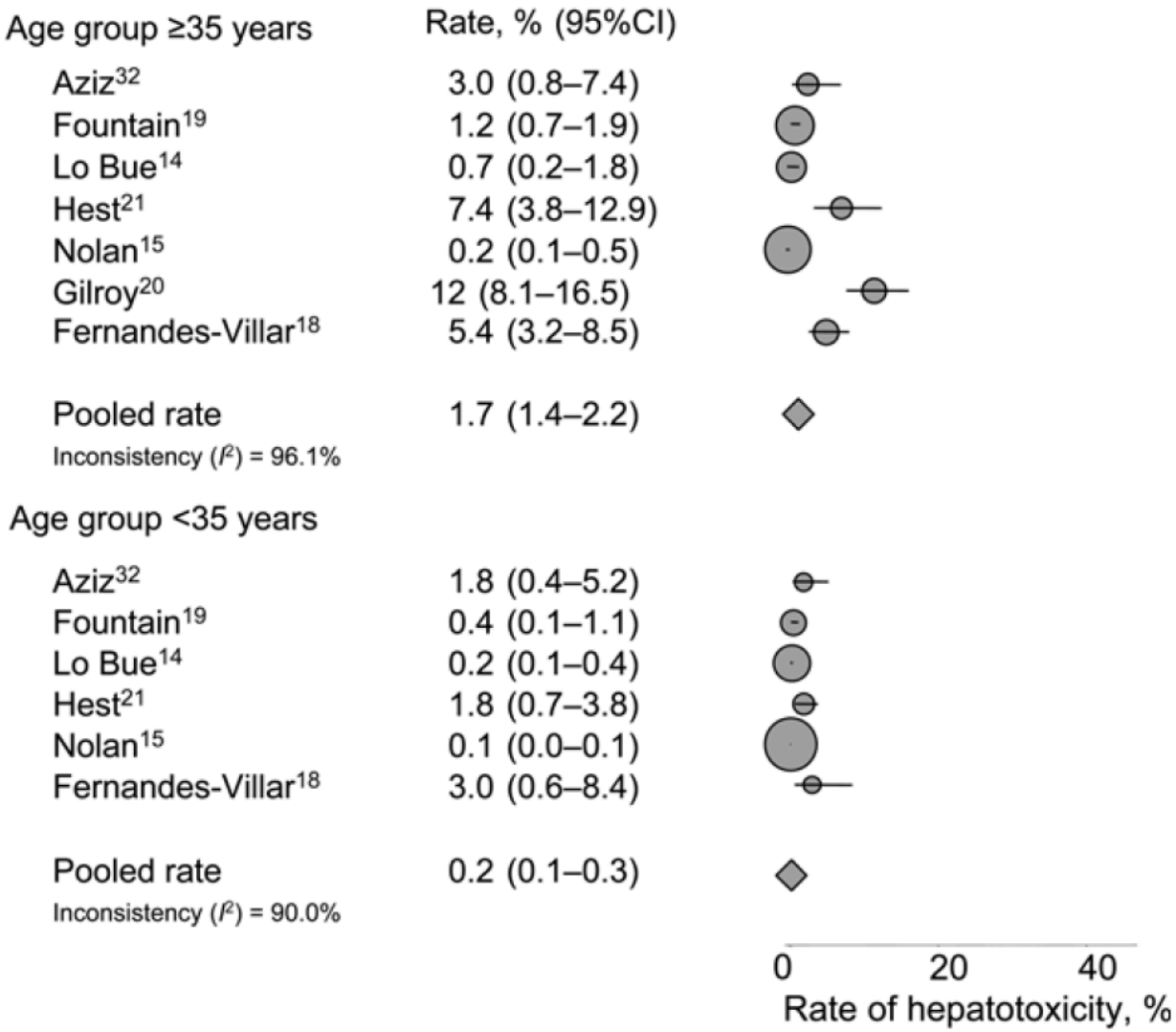
INT J TUBERC LUNG DIS 14(11):1374–1381

Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review

H. Kunst,* K. S. Khan†

> 35 Jahre: 1,7 %

< 35 Jahre: 0,2 %



Unverträglichkeit der Chemoprophylaxe bei TNF-a Patienten

High incidence of intolerance to tuberculosis chemoprophylaxis

Ireland: Out of 132 patients who were commenced on different TNF blockers, only 23 patients (17%) were diagnosed with LTBI and were given prophylaxis as per recommended guidelines. Thirty-nine percent (9 out of 23) of patients discontinued INH because of adverse events.

Table 1 Demographic characteristics of patients who developed intolerance to tuberculosis chemoprophylaxis

Age[a]	Gender	Diagnosis	Anti-TNF	DMARDs	Adverse event	Outcome
47	Male	AS	Etanercept	None	Hepatotoxicity	INH discontinued
64	Male	U.SpA	Adalimumab	None	Hepatotoxicity	INH discontinued
20	Male	JIA	Adalimumab	Methotrexate	Persistent nausea	INH discontinued
67	Female	RA	Adalimumab	Methotrexate	Persistent nausea	INH and rifampicin discontinued
54	Male	AS	Adalimumab	None	Persistent nausea	INH discontinued, and had rifampicin
76	Female	RA	Infliximab	Methotrexate	Non-resolving rash	INH discontinued
40	Male	RA	Adalimumab	Methotrexate	Persistent nausea	INH discontinued, and had rifampicin
49	Male	AS	Adalimumab	None	Persistent nausea and vomiting	INH discontinued
29	Male	AS	Adalimumab	None	Hepatotoxicity	INH discontinued

U.SpA undifferentiated spondyloarthropathy, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *JIA* juvenile idiopathic arthritis

[a] Age in years

Rheumatol Int (2012) 32:33–37

Unverträglichkeit der Chemoprophylaxe bei TNFa Patienten

Isoniazid treatment for latent tuberculosis infection is tolerable for rheumatoid arthritis patients receiving tumor necrosis factor inhibitor therapy

Korea: A total of 312 RA patients including 96 patients (30.9%) who took INH for LTBI were included in this analysis. Thirty-nine patients (12.5%) experienced LFT abnormalities while using TNF inhibitors.

Table 2. The impact of INH treatment on the occurrence of liver function abnormality

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
INH treatment	2.73 (1.38–5.39)	3.01 (1.39–6.48)
Age, yr	0.99 (0.97–1.02)	0.98 (0.95–1.01)
Male sex	3.57 (1.69–7.69)	3.97 (1.69–9.33)
Disease duration	0.99 (0.94–1.03)	0.96 (0.90–1.03)
BMI, kg/m²		
< 18.5	1.00	1.00
≥ 18.5 and < 23.0	1.05 (0.36–3.05)	1.16 (0.35–3.78)
≥ 23.0	1.62 (0.57–4.62)	1.53 (1.02–2.37)
Alcohol drinking	1.19 (0.25–5.58)	
Smoking	1.08 (0.23–5.04)	
DAS28ESR(3)	1.33 (0.91–1.93)	1.55 (1.02–2.37)
No. of previous DMARDs used	1.14 (0.92–1.42)	1.21 (0.92–1.60)
TNF inhibitors		
Etanercept	1.00	1.00
Infliximab	0.40 (0.05–3.10)	0.49 (0.05–4.91)
Adalimumab	0.79 (0.37–1.71)	0.81 (0.34–1.96)
Months of TNF inhibitor use	1.01 (0.99–1.02)	1.01 (0.99–1.02)
Concomitant use of corticosteroid	1.31 (0.48–3.53)	1.09 (0.37–3.23)
Concomitant use of methotrexate	0.42 (0.20–0.89)	0.31 (0.13–0.77)
Concomitant use of NSAIDs	0.59 (0.25–1.38)	0.63 (0.24–1.69)
Concomitant use of acetaminophen	1.40 (0.64–3.05)	1.06 (0.43–2.63)
LFT abnormality when starting TNF inhibitor	2.92 (1.07–7.99)	1.55 (0.45–5.41)
Past history of liver function abnormality	2.18 (0.82–5.80)	1.66 (0.52–5.32)

Rheumatol Int (2012) 32:33–37

Unverträglichkeit der Chemoprophylaxe bei Tofacitinib, ADA bzw. MTX Patienten (MTX macht am meisten Probleme)

Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis

Table 3 Patients in phase III studies who experienced ALT elevations according to study exposure group and isoniazid usage

	>1×ULN n (%)	>3×ULN n (%)	>5×ULN n (%)	>10×ULN n (%)
Isoniazid/tofacitinib* (n=263)	58 (22.1%)	4 (1.5%)	1 (0.4%)	0
No isoniazid/tofacitinib* (n=3614)	550 (15.2%)	35 (1.0%)	7 (0.2%)	2 (<0.1%)
Isoniazid/adalimumab (n=15)	3 (20%)	0	0	0
No isoniazid/adalimumab (n=189)	24 (12.7%)	2 (1.1%)	1 (0.5%)	0
Isoniazid/methotrexate (n=8)	3 (37.5%)	1 (12.5%)	0	0
No isoniazid methotrexate (n=178)	19 (10.7%)	0	0	0

Winthrop KL, et al. Ann Rheum Dis 2016;75:1133–1138.

Impfungen bei rheumatologischen Erkrankungen

EULAR recommendations for vaccination in adult patients with autoimmune infl ammatory rheumatic Diseases 2011

Box 2 Vaccinations to be checked during the initial investigation (by history taking)

Haemophilus influenzae b
Hepatitis A
Hepatitis B
Human papillomavirus
Influenza
Neisseria meningitides
Rubella (for women of childbearing age)
Streptococcus pneumoniae
Tetanus toxoid

Ann Rheum Dis 2011;70:414–422.

2015 American College of Rheumatology Guideline

Table 2. Recommended use of vaccines in patients with RA treatment[1]

RA treatment	Vaccine				
	Pneumo-coccal	Influenza (killed/ inactivated)	Hepatitis B	Human papilloma	Herpes zoster
Before initiating therapy					
DMARD monotherapy	X	X	X	X	X
Combination DMARDs					
TNF inhibitors	X	X	X	X	X
Non-TNF biologics	X	X	X	X	X
While taking therapy					
DMARD monotherapy	X	X	X	X	X
Combination DMARDs	X	X	X	X	X
TNF inhibitors	X	X	X	X	Not recommended
Non-TNF biologics	X	X	X	X	Not recommended

Arthritis Care & Research, DOI 10.1002/acr.22783, VC 2015, American College of Rheumatology

Impfplan Österreich

2017

MINISTERIUM
FRAUEN
GESUNDHEIT

Influenza Impfung für alle immunsupp. Pat. PFLICHT

Indikation

Die Impfung ist jeder Person, die sich schützen will, zu empfehlen.

Besonders dringlich empfohlen ist die Impfung:

- Personen mit erhöhter Gefährdung oder infolge einer chronischen Erkrankung (chron. Lungen-, Herz-, Kreislauferkrankungen (außer Hypertonie), Erkrankungen der Nieren, neurologische Erkrankungen, Stoffwechselkrankheiten (einschließlich Diabetes mellitus) und Immundefekten)[63]
- Schwangeren und Frauen, die während der Influenzasaison schwanger werden wollen[64]
- Kindern ab dem vollendeten 6. Lebensmonat
- Personen im Umfeld von Neugeborenen
- Personen ab dem vollendeten 50. Lebensjahr
- Kindern/Jugendlichen ab dem 7. Lebensmonat bis zu 18 Jahren unter Langzeit-Aspirin-Therapie (Verhütung eines Reye Syndroms). **Es ist zu beachten, dass in diesem Fall eine Lebendimpfung altersunabhängig kontraindiziert ist!**
- stark übergewichtigen Personen (BMI≥40)
- Betreuungspersonen (z.B. in Spitälern, Altersheimen und im Haushalt) und Haushaltskontakte von Risikogruppen (kleine oder kranke Kinder, ältere Personen, Personen der zuvor genannten Gruppen)[65,66]
- Personen aus Gesundheitsberufen
- Personen mit häufigem Publikumskontakt
- Generell Reisenden: Schutz während der Reise (z.B. am Flughafen, im Flugzeug) und am Reiseziel (Influenzasaison tritt auf der Südhalbkugel etwa um ½ Jahr verschoben auf!).

Pneumokokken Impfung für alle immunsupp. Pat. PFLICHT

Personen **ohne vorangegangene Pneumokokkenimpfung mit erhöhtem Risiko** in Abhängigkeit vom Alter bei der Erstimpfung (PNC: konjugierte Pneumokokkenvakzine (10- oder 13-valent), PPV23: 23-valente Polysaccharidvakzine)[135]:

Alter bei Erstimpfung:	Personen mit erhöhtem Risiko[b]	Empfohlene Auffrischungen
Im 1. Lebensjahr[a]	0/nach 2 Monaten/9-12 Monate nach Erstimpfung PNC	1xPPV23 ab dem 3. Lebensjahr[c]
Im 2. Lebensjahr[a]	0/nach 2 Monaten PNC	1xPPV23 ab dem 3. Lebensjahr[c]
Im 3.-5. Lebensjahr[a]	0/nach 2 Monaten PNC	nach ≥8 Wochen 1 x PPV23
Ab 6. Lebensjahr	PNC13/nach 8 Wochen PPV23	Weitere Vorgehensweise bzgl. Auffrischungen ist derzeit nicht entscheidbar und wird von laufenden Untersuchungen abhängen.

[a] Beginn ehestmöglich ab dem vollendeten 2. Lebensmonat. Im Rahmen des Impfprogramms PNC10 für Kinder mit erhöhtem Risiko bis zum vollendeten 5. Lebensjahr kostenfrei.

[b] So früh wie möglich nach Feststellung des erhöhten Risikos mit der Impfserie beginnen (Mindestabstand 8 Wochen zwischen Impfungen), bei elektiver Splenektomie oder Cochlearimplantation und bei Planung einer immunkompromittierenden Therapie sollte die Impfung spätestens 2 Wochen vorher abgeschlossen sein. Eine weitere PNC Impfung sollte nach Splenektomie (vor Krankenhausentlassung) erfolgen[136,137,138].

[c] Mindestabstand zu letzter PNC-Impfung 8 Wochen.

Impfempfehlung Australien bzgl. Influenza und Pneumokokken

A practical approach to vaccination of patients with autoimmune inflammatory rheumatic diseases in Australia

Vaccine	Recommendations	Dosing	Frequency	Cost covered by NIP	Approx. cost if not covered by NIP
Influenza	Annually	Two doses 4 weeks apart for 1st year and then one dose annually	Annually	Yes	NA
Pneumococcus-vaccine-naïve	13vPCV, 23vPPV vaccines	13vPCV first, then 23vPPV after ≥8 weeks	Rpt in 5 years, then 3rd dose at age 65	For adults ≥65 years	Standard co-payment $37.70 or $6.10 for concession card holders
Pneumococcus-previously vaccinated	23vPPV at age 18 or at diagnosis of AIIRD, or 5 years after last dose	23vPPV at diagnosis of AIIRD, or 5 years after last dose	<2 More doses, 5 years apart	For adults ≥65 years	Standard co-payment $37.70 or $6.10 for concession card holders

Impfrate: 85% Influenza und 44% Pneumokokken

A large two-centre study in to rates of influenza and pneumococcal vaccination and infection burden in rheumatoid arthritis in the UK

Table 1 Baseline demographics population

	All $n = 929$	HES linked site only $n = 387$
Age (yrs.)	63.1	64.1
Gender Female n (%)	686 (74.9)	302 (78.1)
DMARDs n (%)	731 (78.7)	305 (78.8)
MTX n (%)	490 (52.7)	223 (57.6)
Biologics n (%)	240 (25.8)	109 (28.2)
Current smoker n (%)	191 (20.6)	54 (14.0)
Comorbidity n (%)	306 (32.9)	127 (32.8)

Table 2 Vaccination status of the study population

Total $n = 929$ $n < 65$ years = 467 $n > 65$ years = 462	Ever offered influenza vaccination	Ever offered pneumococcal vaccination	Received influenza vaccination	Received pneumococcal vaccination
Total n (%)	841 (90.5)	410 (44.1)	798 (85.9)	412 (44.3)
Age <65 years n (%)	421 (90.1)	203 (43.5)	400 (85.7)	207 (44.3)
Age >65 years n (%)	420 (90.9)	207 (44.8)	398 (86.1)	205 (44.4)

Subesinghe et al. BMC Musculoskeletal Disorders (2016) 17:322

Impfrate: 80% Influenza und 50% Pneumokokken

Influenza and Pneumococcal Vaccination Uptake in Patients with Rheumatoid Arthritis Treated with Immunosuppressive Therapy in the UK: A Retrospective Cohort Study Using Data from the Clinical Practice Research Datalink

Table 4. Summary of studies of influenza and pneumococcus vaccination uptake in the UK.

Author	Type of study	N	Disease group	Influenza vaccine uptake	Pneumococcal vaccine uptake
Pradeep et al (2006)	Audit	64	Rheumatoid arthritis	63%	43%
Doe et al (2007)	Audit	169	Rheumatic diseases	79%	34%
Thomas et al (2004)	Audit	111	Rheumatic diseases	70%	33%
Bridges et al (2003)	Audit	129	Rheumatoid arthritis	56% (of those taking MTX (n = 59))	-
Clarke et al (2011)	Audit	71	Rheumatoid arthritis	~70%	-
Saravana et al (2004)	Audit	100	Rheumatic diseases	77%	-
Sowden et al (2007)	Audit	101	Rheumatic diseases	54%-93%	38%-64%
Hmamouchi et al (2015)	Cohort	43 (UK patients)	Rheumatoid arthritis	84%	44%