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BRIEF COMMUNICATION

Infectious risk stratification in multiple sclerosis patients receiving immunotherapy

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Abstract

The increasing number of potent treatments for multiple sclerosis warrants screening for infections. To investigate the prevalence of infections in two independent German patient cohorts with multiple sclerosis/neuromyelitis optica spectrum disorders (NMOSD), we performed a retrospective chart review study of multiple sclerosis/NMOSD patients who underwent testing for infections between 2014 and 2016. We show that 6 out of 80 tested patients (Düsseldorf cohort) and 2 out of 97 tested patients (Münster cohort) had a latent tuberculosis infection; total 3.95%, 95% CI: 2–8%. Our findings suggest that latent tuberculosis infection is frequent (>1%). Screening should be performed before embarking on immunomodulatory therapies to allow treatment and mitigation of the risk of a reactivation.

Introduction

Balancing benefit and risk in modern multiple sclerosis (MS) drug management is crucial. In this context, the reactivation or de novo acquisition of infectious diseases is gaining relevance.[1,2]

This study focuses on the significance of screening for latent tuberculosis infection (LTBI) in MS patients. The possible implications of LTBI have already been reviewed[1,3] but there is a paucity of real-world data including tuberculosis (TB) risk stratification.

Patients and Methods

We conducted a bicentral retrospective chart review study at the MS Centers of the Heinrich-Heine-University Düsseldorf and the University Hospital of Münster. In Düsseldorf, we searched for all MS/NMOSD patients to be started on highly potent immunotherapy between May 2014 and December 2016, while in Münster all patients to be started on dimethyl fumarate or alemtuzumab were investigated between May 2014 and December 2016. In Münster, comprehensive screening for infectious risks was only performed for the cohorts of patients on alemtuzumab and dimethyl fumarate, and only patients with comprehensive screening were included to avoid a selection bias. Thus, from Münster only patients from these cohorts were enrolled. Screening was performed as follows: Tuberculosis (T-Spot.TB Test, Oxford Immunotec (Düsseldorf/Münster)), human immunodeficiency virus (HIV; HIV Ag/Ab Combo, 4J27-30, Abbott (Düsseldorf); ADVIA Centaur HIV Ag/Ab Combo, CHIV, Siemens

Healthcare (Münster)), hepatitis B (HBsAg qualitative II, 2G22-30 and Anti-HBc II, 8L44-30, Abbott (Düsseldorf); ADV IA Centaur HBsAgII HBsII-Test and ADVIA Centaur-HBc-gesamt-Test, Siemens Healthcare (Münster)), hepatitis C (Anti-HCV, 6C37-30, Abbott (Düsseldorf); ADVIA Centaur HCV-Test, aHCV, Siemens Healthcare (Münster)), *Varicella zoster* virus (VZV; Liaison VZV IgG, Fa. DiaSorin (Düsseldorf/Münster)), *Treponema pallidum* (Treponema CLIA, Liaison Treponema Screen, Fa. DiaSorin (Düsseldorf); TPPA/FTA/RPR IFT, Mast Diagnostica (Münster)), and *John Cunningham* polyomavirus (JCV, Stratify® assay (Düsseldorf/Münster)). The study was approved by the ethics committee in Düsseldorf (registry number 5598).

Results

Results of virological, *Treponema pallidum* and IFN-γ release assay (IGRA) testing

Of the 80 IGRA-tested patients in Düsseldorf, 58 (72.5%) were female and 22 (27.5%) were male. Mean age was 41.9 years. The patients were diagnosed with RRMS (52; 65%), SPMS (19; 23.7%), PPMS (6; 7.5%), and NMOSD (3; 3.8%). Mean EDSS was 4. IGRA testing (Table S1) revealed a reactive result in 6 of 80 (7.5%, 95% CI: 3–16%) patients (patients *D2, D20, D21, D33, D40, D80)*. Active TB was ruled out by routine blood work-up, chest X-ray, microbiological testing of sputum, and urine. LTBI treatment was performed according to the recommendations of the Centers for Disease Control and Prevention (CDC)[4] or Blumberg et al.[5] IGRA testing revealed a borderline result in 3 of 80 (3.8%, 95% CI: 0.8–11%) patients. All retests after 3–4 weeks were negative.

All patients in Düsseldorf who underwent screening for hepatitis B/C, HIV, and *Treponema pallidum* were tested negative for an acute infection or a prior exposure to the pathogen. The presence of anti-HBc-IgG indicating recovery and immunity after a previous hepatitis B infection was detected in one patient. Of the 102 patients screened for VZV, 3 (2.9%) patients presented findings indicating a lack of immunity against the virus (VZV IgG <100.0 IU/mL). Of all patients tested for JCV serostatus (n = 430), 139 were negative, 72 were positive with an index value <0.9, 51 were positive with an index value 0.9–1.5, and 168 were positive with an index value of >1.5. No case of progressive multifocal leukoencephalopathy (PML) occurred during the observation period at the MS center in Düsseldorf. An overview of the Düsseldorf cohort results is provided in Table 1.

To investigate whether the rather high LTBI rate in the Düsseldorf cohort might have been specific to Düsseldorf, the capital of the federal state of North Rhine Westphalia which is located in the largest urban industrial area of Germany, we chose to also investigate the LTBI rates in Münster, a smaller city located in the more rural area of Westphalia. Of the 97 IGRA-tested MS patients (96 RRMS, 1 SPMS) in Münster, 57 (58.8%) were female and 40 (41.2%) were male. Mean age was 35.8 years. Mean EDSS was 2.45. In this cohort, we identified one reactive case (*M97*; 1%, 95% CI: 0.01–6%) and obtained one

Table 1. Results of virological, *Treponema pallidum* and IGRA testing, Düsseldorf cohort.

Pathogen	Test used	Number of tests	Results
TB	IGRA (T-Spot)	80	71 not reactive (88.7%) 3 borderline (3.8%) 6 reactive (7.5%)
Hepatitis B	HBsAg, Anti-HBc-IgG CMIA	71 HBsAg 63 Anti-HBc-IgG	71 HBsAg negative (100%) 62 Anti-HBc-IgG negative (98.4%) 1 Anti-HBc IgG positive (1.6%)
Hepatitis C	CLIA	72	All negative
HIV	CLIA	43	All negative
VZV	VZV IgG CLIA	102	99 positive (97.1%) 3 VZV IgG <100.0 IU/mL (2.9%)
T. pallidum	CLIA	41	All negative
JCV	Stratify® assay	430	139 negative (32%) 72 positive with index value <0.9 (17%) 51 positive with index value 0.9–1.5 (12%) 168 positive with index value >1.5 (39%) 0 PML cases during observational period

TB, tuberculosis; IGRA, IFN-γ release assay; CMIA, carbonylmetalloimmunoassay; CLIA, chemoluminescence immunoassay; HIV, *Human Immunodeficiency* virus; VZV, *Varicella zoster* virus; *T. pallidum*, *Treponema pallidum*; JCV, *John Cunningham* polyomavirus; PML, progressive multifocal leukoencephalopathy.

borderline result (*M59*) and one reactive result (*M49*) which were both later refuted by negative results in the confirmation test (Table S2). Active TB was ruled out and treatment was performed as described above. In Münster, all patients who underwent screening for hepatitis B/C, HIV, and *Treponema pallidum* were tested negative for an acute infection or a prior exposure to the pathogen. The presence of anti-HBc-IgG indicating recovery and immunity after a previous hepatitis B infection was detected in two patients and all patients screened for VZV presented findings indicating immunity. Of all patients tested for JCV serostatus ($n = 68$), 22 were negative, 6 were positive with an index value <0.9, 4 were positive with an index value 0.9–1.5, 22 were positive with an index value of >1.5, and 14 were positive with an unknown index value. Two cases of progressive multifocal leukoencephalopathy (PML) occurred during the observation period at the MS center in Münster.

An overview of the Münster cohort results is provided in Table 2.

In total, of 177 patients tested with an IGRA in Düsseldorf and Münster, 7 had a reactive result (3.95%, 95% CI: 2–8%).

LTBI treatment

After testing positive, patients *D20*, *D21*, *D33*, *and D80* received rifampicin (RMP) 600 mg/d plus isoniazid (INH) 300 mg/pyridoxine 10–25 mg/day for 3 months and patients *D2* and *D40* received INH 300 mg/pyridoxine 20 mg/day for 9 months. Patient *M97* declined treatment.

Patients *D21*, *D33*, and *D80* in the RMP/INH/pyridoxine group received the medication continuously for 3 months, patient *D20* due to poor tolerability (dizziness, nausea) was switched to a 9-month INH 150 mg/pyridoxine 20 mg per day regimen. In parallel, patient *D20* started alemtuzumab therapy after 1 month of TB therapy.

Patient *D2* switched from INH 300 mg/pyridoxine 20 mg/day to a 6-month RMP 600 mg/pyrazinamide (PZA) 750 mg/day regimen due to paresthesia of both legs. Since the paresthesia remitted a few days after stopping INH, nerve conduction studies for isoniazid-induced polyneuropathy were not performed. In parallel, this patient was started on off-label rituximab and after completing the 6-month TB therapy, switched to alemtuzumab. Patient *D40* was also started on a rituximab therapy parallel to LTBI therapy. After completion of TB treatment, diagnostic work-up (routine blood work-up, chest X-ray, microbiological testing of sputum and urine) revealed no evidence of TB reactivation in any of the six patients. A follow-up IGRA after treatment remained – as expected – reactive.

An overview of the diagnostic work-up and treatment is provided in Figure 1.

Discussion

LTBI is the most prominent infectious risk factor besides JCV in our cohorts. We observed an expected[6] number of patients with LTBI. Due to the high awareness of the risk for developing a progressive multifocal leukoencephalopathy (PML) in the context of highly active MS therapy,

Table 2. Results of virological, *Treponema pallidum* and IGRA testing, Münster cohort.

Pathogen	Test used	Number of Tests	Results
TB	IGRA (T-Spot)	97	95 not reactive (98%) 1 borderline (1%) 1 reactive (1%)
Hepatitis B	HBsAg, Anti-HBc-IgG CLIA	96 HBsAg 96 Anti-HBc-IgG	96 HBsAg negative (100%) 94 Anti-HBc-IgG negative (98%) 2 Anti-HBc IgG positive (2%)
Hepatitis C	CLIA	97	All negative
HIV	CLIA	97	All negative
VZV	VZV IgG CLIA	78	All positive
T. pallidum	IFT	73	All negative
JCV	Stratify® assay	68	22 negative (32.5%) 6 positive with index value <0.9 (9%) 4 positive with index value 0.9–1.5 (6%) 22 positive with index value >1.5 (32.5%) 14 positive with unknown index value (20%) 2 PML cases during observational period

TB, tuberculosis; IGRA, IFN-γ release assay; CLIA, chemoluminescence immunoassay; HIV, *Human Immunodeficiency* virus; VZV, *Varicella zoster* virus; *T. pallidum*, *Treponema pallidum*; JCV, *John Cunningham* polyomavirus; PML, progressive multifocal leukoencephalopathy.

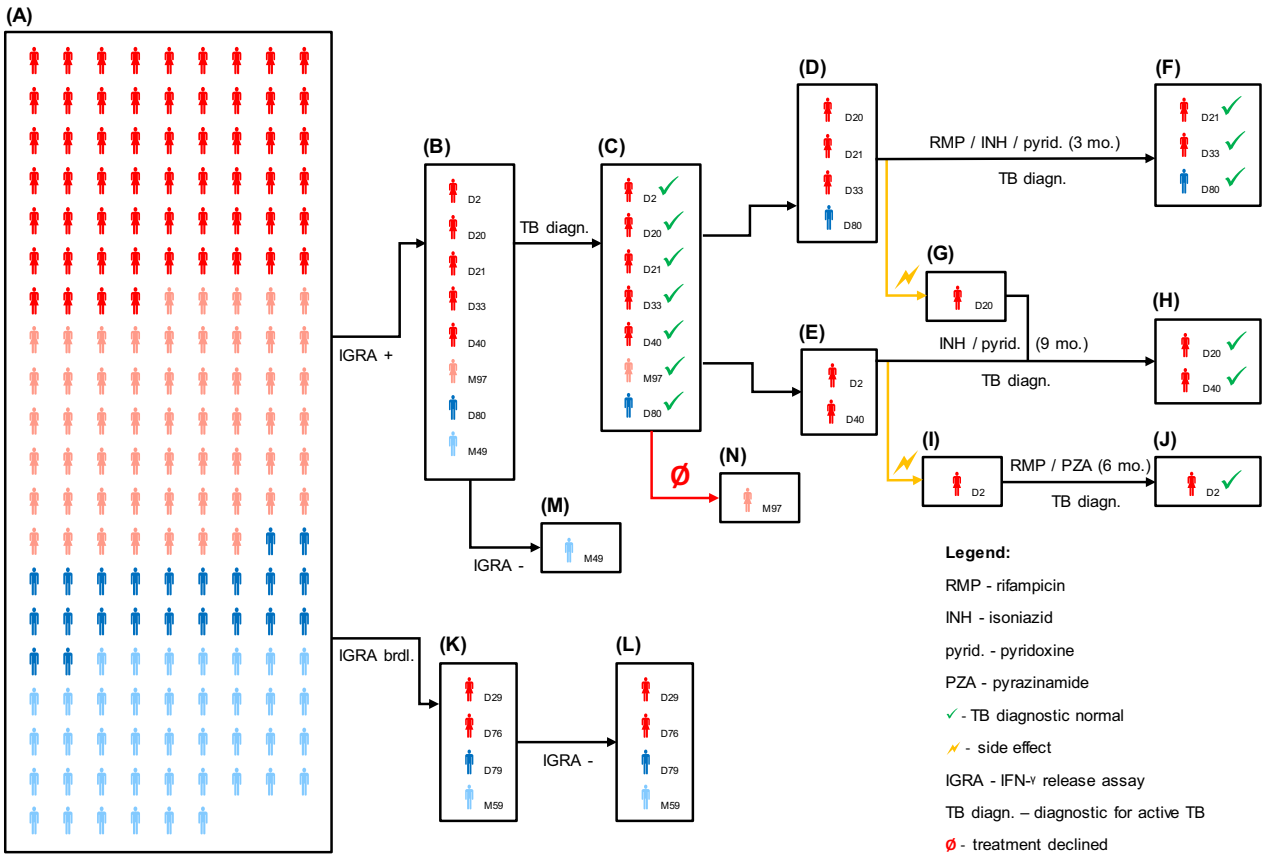

Figure 1. IGRA screening und LTBI treatment of the Düsseldorf (bold red female, bold blue male) and Münster (light red female, light blue male) cohort (lower case indicates patient ID). One hundred and seventy-seven patients were screened with an IGRA (A), eight patients had a reactive result (B). Of these eight patients with reactive IGRA, seven patients had normal routine TB diagnostic (C) and therefore LTBI and one reactive result was later confirmed as negative (M). Of these seven LTBI patients, four received RMP/INH/pyridoxine (D), two patients INH/pyridoxine (E), and one patient declined therapy (N). Of the four patients in (D), three patients continued the regime for 3 months and one patient switched to a 9-month INH/pyridoxine regime due to side effects (G). Two of the six LTBI patients started with INH/pyridoxine treatment (E), but one patient switched to a 6-month RMP/PZA regime (I) due to side effects. Routine TB diagnostic after LTBI treatment was normal (F, H, J); Four patients had a borderline (brdl.) IGRA result (K), retesting after 3–4 weeks was normal (L).

namely natalizumab, more patients have been screened for JCV antibodies. However, our data suggest that possibly also LTBI-reactivation may be a relevant risk especially in the context of highly active immunotherapies.

Clinically relevant TB infections have been associated with a number of MS treatments: While an increased risk of LTBI-reactivation has been published regarding patients treated with alemtuzumab,[7,8] daclizumab[9], natalizumab[10], and glucocorticoids,[11] fingolimod treatment was thus far not associated with an increased rate of manifest TB infections. With CD20-depleting therapies (rituximab, ocrelizumab), a more complex picture evolves: The TB infection rate does not seem to be increased in relapse-remitting[12,13] and primary-progressive[14,15] MS disease nor has this been noted in oncological patient populations undergoing extended rituximab therapy for lymphoma.[16] However, TB cases have been reported in rheumatoid arthritis patients treated with ocrelizumab in combination with methotrexate.[17]

There is a tendency toward a higher LTBI rate in Düsseldorf (7.5%) than in the independent Münster cohort (1.03%). This could be a reflection of the higher incidence of tuberculosis in Düsseldorf: In 2015, 385 cases of tuberculosis were reported in Düsseldorf and 144 in Münster (SurvStat@RKI). Thus, in our study, LTBI seems to be more relevant in the urban cohort than in the rural cohort. However, the confidence intervals of the two cohorts overlap, so a significant difference of the LTBI rate cannot be postulated. Several of our patients were already on active immunomodulatory treatments at the time of testing and some of these therapies may cause false-negative IGRA results. It is

therefore possible that the LTBI rate might even be higher. As IGRA was the primary TB test used in all patients, booster effects due to prior skin testing as common reasons of false-positive results were not an issue in our cohorts.

Three of the six IGRA-reactive patients from Düsseldorf were immigrants from countries with a higher prevalence of TB than Germany (the Balkans, Turkey, and Russia). Similarly, the patient from Münster was from Russia. The LTBI prevalence in our cohort is similar to that expected for Western Europe[6]. With regard to the current migration development in Europe, manifest tuberculosis is expected to become more relevant in patients with immunotherapy and thus LTBI screening will become more important in the future.

Real-world data from MS clinics at two German tertiary referral centers indicate that LTBI affects a relevant proportion of MS patients and is an important concern. In line with existing recommendations, screening should be performed before initiation of daclizumab and alemtuzumab treatment. According to the Rituximab Consensus Expert Committee,[18] there is no evidence to support screening patients before initiation of CD20-depleting monotherapy (rituximab, ocrelizumab). However, given the high LTBI prevalence in our cohort and the previous complications in patients with ocrelizumab combination therapy, IGRA testing may be considered when a long-term B-cell depleting therapy is planned. In patients with pertinent symptoms under immunotherapy, TB reactivation should be taken into account. Larger observational studies are needed to assess the reactivation risk in various treatment regimens and geographies.

Author Contribution

Jonas Graf – Study concept/design, acquisition/analysis/interpretation of data, drafting of the manuscript. Verena I Leussink – critical revision of the manuscript. Thomas Dehmel – critical revision of the manuscript. Marius Ringelstein – critical revision of the manuscript. Norbert Goebels – critical revision of the manuscript. Ortwin Adams – critical revision of the manuscript. Colin R MacKenzie – critical revision of the manuscript. Clemens Warnke – critical revision of the manuscript. Torsten Feldt – critical revision of the manuscript. Anna Lammerskitten – acquisition of data. Luisa Klotz – acquisition/analysis/interpretation of data, drafting and revision of the manuscript. Sven Meuth – critical revision of the manuscript. Heinz Wiendl – critical revision of the manuscript. Hans-Peter Hartung – critical revision of the manuscript. Orhan Aktas* – Study concept/design, critical revision of the manuscript. Philipp Albrecht* – Study concept/design, acquisition/analysis/interpretation of data, drafting and revision of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest related to the work presented. The following financial disclosures are unrelated to the work: Jonas Graf – reports no disclosures. Verena I Leussink – has received speaker honoraria as well as travel reimbursements and financial support for research from Biogen and Novartis. Thomas Dehmel – has no present financial ties to any commercial companies and has received no finances in the previous 2 years. Meanwhile, TD started working for Novartis Pharma. Marius Ringelstein – has received consulting and speaker honoraria as well as travel reimbursements from Bayer Healthcare, Biogen, Genzyme, TEVA, Merz, and Novartis. Norbert Goebels – received, with approval by the Rector of the Heinrich-Heine-University, travel support to scientific conferences from Bayer, Biogen, Genzyme, Novartis; research support (unrelated to this manuscript) from Novartis; honoraries for lectures (unrelated to this manuscript) from Biogen. Ortwin Adams – reports no disclosures. Colin R MacKenzie – has no present financial ties to any commercial companies and has received no finances from commercial companies in the previous 5 years. Clemens Warnke – consulting and/or research funding: Biogen, Novartis, TEVA. Torsten Feldt – reports no disclosures. Anna Lammerskitten – reports no disclosures. Luisa Klotz – has received honoraria for lecturing and serving on advisory boards as well as travel expenses for attending meetings and financial research support from Novartis, Biogen, Genzyme, and the DFG. Sven Meuth - has received honoraria for lecturing, travel expenses for attending meetings and financial research support from Almirall, Bayer Health Care, Biogen, Diamed, Genzyme, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, and Teva. Heinz Wiendl – is member of Scientific Advisory Boards/Steering Committees for Bayer Healthcare, Biogen Idec, Sanofi Genzyme, Merck Serono, Novartis, Roche, and Teva. He received speaker honoraria and travel support from Bayer Vital GmbH, Bayer Schering AG, Biogen, CSL Behring, EMD Serono, Fresenius Medical Care, Genzyme, Merck Serono, Omniamed, Novartis, and Sanofi Aventis and Teva. He received compensation as a consultant from Biogen Idec, Merck Serono, Novartis, Omniamed, Roche, and Sanofi Genzyme. He has got research supports from Bayer Healthcare, Bayer Vital, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Sanofi US, and Teva Pharma as well as German Ministry for Education and Research (BMBF), German Research Foundation (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation,

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Screening for Tuberculosis, detailed overview of IGRA-tested patients in Düsseldorf (D).
Table S2. Screening for Tuberculosis, detailed overview of IGRA-tested patients in Münster (M).

