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Multiple sclerosis treatment and infectious issues: update 2013

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Summary

Immunomodulation and immunosuppression are generally linked to an increased risk of infection. In the growing field of new and potent drugs for multiple sclerosis (MS), we review the current data concerning infections and prevention of infectious diseases. This is of importance for recently licensed and future MS treatment options, but also for long-term established therapies for MS. Some of the disease-modifying therapies (DMT) go along with threats of specific severe infections or complications, which require a more intensive long-term monitoring and multi-disciplinary surveillance. We update the existing warning notices and infectious issues which have to be considered using drugs for multiple sclerosis.

Keywords: disease-modifying treatment, immunosuppression, infection, multiple sclerosis, side effects

Introduction

Multiple sclerosis (MS) is an immune-mediated illness [1,2] with clinically heterogeneous illness manifestations [3]. The immunomodulating treatment of MS is becoming more complex, with a growing number of potent therapeutics with relevant side effects [4–9]. The individual therapies employed in the treatment of MS have a variety of distinctive effects on the immune system and thus influence the risks of suffering from specific infections during the related therapies in a number of ways [10] (Table 1). In the following we will discuss the immunotherapeutics currently available for MS as well as the anticipated new immunotherapeutics with their postulated action mechanisms and will focus on the infection-related side effects from a clinical viewpoint (Tables 1 and 2).

Relapse treatment

Glucocorticosteroids (GCSs) are used mainly to treat MS relapses in high doses (0·5–3 g per day over 3–5 days) [11–13]. In individual cases they are also used for patients with secondary-chronic progressive MS (SP-MS) and primary-chronic progressive MS (PP-MS) as cyclic pulse therapies, e.g. every 3 months [14,15]. GCSs bring about a suppression of the inflammatory reaction. On one hand, they influence cellular immune processes by apoptotic induction and inhibition of the migration of immune cells, while on the other hand they influence humoral immune processes such as the reduction of proinflammatory cytokines [interleukin (IL)-2, interferon (IFN)-γ and tumour necrosis factor (TNF)-α] [16]. Additional postulated mechanisms of action relate to the inhibition of arachnoid acid metabolites, inhibition of the degranulation of lysosome enzymes, decrease in vascular dilatation, fibrin deposition and restoration of the blood–brain barrier [17]. Infection-related aspects of the therapy (Table 1), such as masking of clinical signs of infection or the exacerbation of latent infection, have been known for many years in the context of MS therapy [18,19].

After initial publications by Weinshenker [20] and Keegan [21], plasmapheresis is currently used as a

Table 1. Infectious aspects of immunomodulating and immunosuppressive therapies for multiple sclerosis (MS).

Active substance[†]	Trade name	Warning notices[‡]	Adverse events and side effects[‡]
Methylprednisolone	e.g. Urbason	• Critical use under the following conditions; add calculated anti-infective treatment where appropriate: ◦ Acute viral infection (e.g. herpes zoster, herpes simplex, varicella, keratitis herpetica) ◦ Hbs-antigen-positive chronic active hepatitis ◦ Up to 8weeks before and 2 weeks after live vaccines ◦ Systemic mycosis and parasitosis (e.g. nematodes) ◦ Poliomyelitis ◦ Lymphadenitis following BCG-vaccination ◦ Acute and chronic bacterial infections ◦ History of tuberculosis (cave: reactivation), treat latent TB infection • Steroid-associated immunosuppression increases risk of opportunistic infections • Aggravated courses of viral diseases (chickenpox, measles) possible • Immunosuppressed children and adults without history of chickenpox or measles are at increased risk: consider post-exposition prophylaxis	• Increased risk of viral infections of potentially severe or fatal course of disease (varicella, herpes simplex and during viraemic phase of herpes zoster) • Masking of infections • Exacerbation of latent infections
Interferon beta-1a	Avonex	• Anti-viral effects of type I interferons *per se* documented • No special warning notices in the context of infection	Abscess formation at injection-site, incidence unclear
	Rebif	• No special warning notices in the context of infection • Anti-viral effects of type I interferons *per se* documented • In case of injection-site lesions follow-up by physician	Occasional abscess formation at injection site (incidence in relevant trials between >1/1000 to <1/100) Post-marketing reports (incidence unknown): systemic infections including parasitosis and infections at injection site
Interferon beta-1b	Betaferon, Betaseron	• Contains human albumin causing potential risk of transmission of viral diseases • Theoretical risk of transmission of Creutzfeld–Jacob disease (CJD) cannot be ruled out • Anti-viral effects of type I interferons *per se* documented • In case of injection-site lesions follow-up by physician • In case of neutropenia high frequent/low threshold search for infection	Analysis of 1093 patients (placebo 965) from four pooled trials: • Manifestation of any infection: 6–14% (3–13%) • Abscess formation: 0–4% (1–6%), no statistically significant differences • Sinusitis: 4–36% (6–26%), no statistically significant differences Analysis of 652 patients (placebo 534) from two pooled trials • Upper airway infections: 3–18% (2–19%), no statistically significant differences [130–132]
	Extavia	• Contains human albumin causing potential risk of transmission of viral diseases • Theoretical risk of transmission of CJD cannot be ruled out • Anti-viral effects of type I interferons *per se* documented • In case of injection-site lesions follow-up by physician • In case of neutropenia high frequent/low threshold search for infection	See Betaferon/Betaseron
Glatiramer acetate	Copaxone	• No special warning notices in the context of infection	Analysis of 269 patients (placebo 271) for 35 months [42,133] Frequent (>1:100, <1:10): • Bronchitis, cough, rhinitis • Herpes simplex (>2% more frequent compared to placebo) • Vaginal candida mycosis (>2% more frequent compared to placebo) • Cystitis Occasional (>1:1000, <1:100): • Pyelonephritis
Fingolimod (FTY 720)	Gilenya	Contraindications: • Immunodeficiency syndrome • Opportunistic infections • Treatment-associated Immunosuppression • Active infections (acute and chronic hepatitis or tuberculosis) Caveats: • Normal blood cell count, not older than 6 months before treatment initiation • Pause treatment if lymphocyte count $<0{\cdot}2 \times 10^9$/l • No treatment initiation with ongoing acute infection • Test for VZV antibodies if patients have no history of chicken-pox or VZV vaccination • in case of missing VZV-antibodies consider vaccination and postpone treatment initiation for 30 days • FTY-treatment can increase risk of infections • In case of infection-associated symptoms perform appropriate testing and consider treatment • Consider FTY treatment interruption in case of severe infection and re-evaluate indication • Enforced surveillance respective infections up to 2 months after FTY treatment • Keep patients informed with respect to increased risks of infections	Side effects [48,49]: Very often (>1:10): • Influenza infection Frequent (>1:1000, <1:10): • Herpes virus-infection • Bronchitis • Sinusitis • Gastroenteritis • Tinea infection Occasional (>1:1000, <1:100): • Pneumonia Overall similar rates of infections (69 *versus* 72%) and severe infections (1·6 *versus* 2·6%) in MS patients comparing pooled 0·5 mg and 1·25 mg FTY *versus* placebo [48]. Lower airway infections, especially bronchitis and pneumonia more often with FTY treatment. Two cases of fatal herpes infection (1·25 mg FTY/day): • Delayed start of acyclovir treatment in a case of HSV encephalitis • Primary disseminated VZV infection in context of former missing exposition to VZV and concurrent high-dose steroid course for MS relapse treatment Third case of disseminated VZV-infection 39 months after initiation of FTY-treatment during follow up of TRANSFORMS [134]
Teriflunomide	Aubagio	Contraindications: ◦ Immunodeficiency ◦ Disturbances of bone marrow function ◦ Severe and uncontrolled infections • Patients may be more likely to get infections including opportunistic infections • Single case of fatal sepsis following pneumonia due to *Klebsiella* spp. infection. • Fatal cases *of Pneumocystis jiroveci* pneumonia and aspergillosis with underlying rheumatoid arthritis and concomitant immunosuppressive treatment • Reactivation of CMV (cytomegalovirus)-associated hepatitis	• Delay treatment initiation in case of active acute or chronic infections • In case of severe infection consider discontinuation of treatment and /or procedure for accelerated elimination • Keep patients informed about likelihood for infections and necessity regular follow-up • Screen for tuberculosis (TB) before treatment initiation, use standard TB treatment regimen where required
Natalizumab	Tysabri	• Exclude immunosuppression before treatment • Increased risk for opportunistic infections • Risk of progressive multi-focal leucencephalopathy (PML), worldwide 372 cases from 115·365 natalizumab-exposed patients, 83 deaths (23%) (as of 4 June 2013 [135])	Analysis of placebo-controlled trials with 1617 patients (placebo 1135) and 2-year treatment duration Often (>1:1000, <1:10): • Urinary tract infection • Nasopharyngitis Single case of uncomplicated cryptosporidium-associated diarrhoea Single case of fatal herpes encephalitis PML (two cases in MS trials, single case in Crohn's disease trial)

Table 1. *Continued*

Active substance[†]	Trade name	Warning notices[‡]	Adverse events and side effects[‡]

Mitoxantrone	e.g. Ralenova	• Contraindications:
		  ○ Severe acute infections
		  ○ Neutrophil granulocyte count <1500 cells/mm^3 (exception: treatment of acute non-lymphocytic leukaemia)
		• Before treatment initiation exclude or treat infection
		• Treatment steering and dose adjustment following blood cell count post last or pre new treatment cycle having regard to recent history of infection
		• *In-vitro* analysis showed no *per se* anti-microbiotic effect of mitoxantrone in concentrations less than 10 mg/l
			Side effects:
			Very often (>10%):
			• Urinary tract infections
			• Upper airway infection
			Unknown incidence:
			• Overall infections
			• Pneumonia
			• Sepsis
			• Opportunistic infections

Off-label setting: Rituximab	MabThera	Contraindications: • Active and/or severe infections (e.g. tuberculosis, sepsis, opportunistic infections) • Severe immunodeficiency (e.g. hypogammaglobulinaemia, reduced CD4- or CD-8 cell count) • Extraordinary attention if neutrophil granulocyte count <1·5 × 10^9/l. • Precaution in case of history of recurrent or chronic infections or other concomitant diseases, increasing the risk of infection • Clinical surveillance regarding infections between treatment cycles • Sufficient testing and treatment of infection following application if required	• Reactivation of hepatitis B including fulminant courses • Very rare manifestation of progressive multifocal leucoencephalopathy (PML) in patients with non-Hodgkin lymphoma (NHL), post-launch • PML cases after off-label use in systemic lupus erythematosus and vasculitis and precedent or concomitant immunosuppressive treatment according to surveillance reporting system. • No PML-reports with patients suffering from rheumatoid arthritis (RA) • PML manifestation in patients with autoimmune-disease without rituximab exposition Rheumatological indication: • Overall infection rate 0·9 per patient-year • Predominance of upper airway and urinary tract infections • Rate of relevant, partly fatal infections 0·05 per patient-year Phases II and III trails in RA (R-MTX *versus* MTX; *n*: 540 *versus* 398) [136–138]: • Any infection: 37–41% *versus* 30–37% • Urinary tract infections: 5–6 *versus* 4–8% • Upper airway infections: 13–16 *versus* 12–15% • Lower airway infections/pneumonia: 3–4% *versus* 2–5% Haematological indication: Side effects according to clinical trials (*n*: 356 NHL patients, monotherapy): • Deprivation of B cells in 70–80% of patients • Decrease of immunoglobulins only in rare cases • Overall 30·3% infections, independent of causal connection • 3·9% severe (grade 3 and 4) infections including sepsis (1·4% during and 2·5% after treatment) Post-marketing-surveillance: • Very rare (<1:10·000): severe virus infections: manifestation, reactivation and deterioration of herpes virus group-associated (CMV, VZV HSV) diseases, JC-virus and hepatitis C virus
Azathioprine	e.g. Imuran	Contraindications: • Treatment initiation with pre-existing severe infection under strict risk–benefit consideration only • Immunization with live vaccines • Immunosuppression can cause severe VZV infections (chickenpox, herpes zoster) • Check history of VZV infection, consider testing for previous exposition • Consider passive VZV immunization in VZV antibody-negative patients with contact to patients with chickenpox or herpes zoster	Occasional (>1:1·000, <1:100) • Viral and bacterial infections as well as mycosis • Increased risk of infection including severe and atypical manifestations of VZV or other infectious diseases, especially under combination therapy with glucocorticosteroids
Cyclophosphamide	e.g. Cytoxan	Contraindications: • Active infections • Cystitis • Rehabilitate from infection before treatment initiation • Accurate oral hygiene • Blood cell count and urinary sedimentation test on a regular basis • Strict monitoring of patients with pre-existing hepatitis because reactivation of hepatitis after cyclophosphamide treatment reported • Mesna-prophylaxis (reduction of urinary tract toxicity and secondary infections)	• Interstitial pneumonia and other infections in the context of conditioning treatment in haematology • Secondary colonization following initially sterile haemorrhagic cystitis
IVIg	e.g. Octagam	• Transmission of possibly unknown infectious agents cannot be ruled out when using drugs deriving from biological material/human donors • Existing inactivation and elimination procedures might be of restricted value for non- or uncoated viruses	Infection risk: see warning notices

[†]Not all substances listed here are licensed for the treatment of MS; some are given on an 'off-label use' basis. [‡]Warning notices and side effects following the current European and American prescribing information as available from the manufacturer (Status 06/2013). Hbs antigen: hepatitis B surface antigen; BCG: Bacillus Calmette–Guérin; VZV: varicella zoster virus; RA: rheumatoid arthritis; MTX: methotrexate; HSV: herpes simplex virus; JC virus: John Cunningham virus; IVIg: intravenous immunoglobulin.

therapeutic option in the context of the escalation therapy in cases of steroid non-responsive relapses [22]. In MS relapse escalation therapy five sessions of plasmapheresis (or eight, if necessary) are generally carried out. In particular, due to the pathophysiological importance of antibodies and complementary factors in the pathogenesis of MS, or at least in the case of special subgroups of patients [23], the removal or reduction of antibodies by means of plasmapheresis or immunoadsorption follows an immunological rationale [24,25]. In its methodical technical implementation (positioning of central venous catheters) as well as from the immunomodulating aspect (removal of the immunoglobulin fraction), this invasive therapy holds at least potentially infection-related risks [26]. A wide range of infection-related complications have been reported in the literature. An older and smaller case study described life-threatening infections in five of eight patients treated with immunosuppressants for rapid progressive

Table 2. Infectious aspects and risks of upcoming multiple sclerosis (MS) therapies.

Active substance	Trade name	Infectious side effects[†]	Infectious issues (monitoring, prophylaxis)
Alemtuzumab	Lemtrada	• Increased rates and risks for infections (urinary tract infections, nasopharyngitis, upper airway infections) • New manifestation and relapse of herpes • Single cases of tuberculosis (cave: endemic regions)	• Medical surveillance, inform patients about increased risks and warning signs • Where necessary blood and/or microbiological tests • Prophylactic aciclovir application for 30 days • Testing for tuberculosis before and where necessary during treatment

BG-12/dimethyl fumarate (DMF)	Tecfidera	• Hitherto no relevant infectiological safety data, especially no progressive multi-focal leucoencephalopathy (PML) cases published
		• No case of PML in 2600 MS patients treated with BG-12 for up to 4 years [60]
		• Safety issues following Fumaderm® treatment of psoriasis (mixture of dimethylfumarate and ethylhydrogenfumarate, licensed in Germany since 1994):
		  • Case report: PML in 74-year-old male suffering from psoriasis after 3 years of treatment [58]
		  • Case report: 42-year-old female after 5 years of treatment [59]
		  • Two further cases of PML following treatment of patients having other well-known risk factors of PML [60]
		  • Two safety reports of PML cases to the German health authorities 2010 in the context of Fumaderm® treatment, one of these is already published (see above) [58,61]
		  • Case of Kaposi sarcoma (HHV-8 infection associated) after Fumaderm® treatment [139]
		  • Case of nocardiosis due to lymphopenia after Fumaderm® treatment [140]
		  • Concerning Fumaderm® treatment whole blood cell counts during treatment are recommended on a regular basis [141]
			• To date, no specific action recommended

Laquinimod	?	• Hitherto no relevant infectious safety data	• To date, no specific action recommended
Daclizumab	Zenapax (until 2007 in the US; until 2009 in EU; license withdrawal independently due to safety concerns)	• Hitherto no relevant infectious safety data	• To date, no specific action recommended

[†]Status 06/2013.

glomerulonephritis [27]. Subsequent studies report hardly any infection-related problems [28,29]. Risks of infectious complications may derive from the venous puncture and central venous catheters for the necessary plasma exchange, occurring at a rate of 2·9–5·5% of all patients [30,31]. A series of cases with 1283 plasmaphereses undertaken on 79 patients with neurological illnesses reported no case of death and no cases of a transfer of hepatitis B or C, or of HIV [30]. In a further investigation, during 2502 plasmaphereses undertaken on 335 patients with neurological illnesses, no single case of post-plasmapheresis infection was found [32]. In another series of 154 plasmaphereses undertaken on 17 neurological patients again no infection-related complications were found [33].

A necessary substitution of fresh-frozen plasma leaves a residual risk of transfer of viral agents in plasma exchange [34,35].

First-line therapy (established basic therapies)

During previous years, beta-IFNs played a major role in the basic therapy of relapsing–remitting multiple sclerosis (RR-MS) and can also be used to treat clinically isolated syndromes (CIS). IFN-β-1a and -1b preparations are used in the treatment of MS. IFN-β-1a is applied either once a week intramuscularly (i.m.) (30 μg, Avonex®) or three times a week subcutaneously (s.c.) (22 or 44 μg, Rebif®). IFN-β-1b (Betaseron®/Betaferon®/Extavia®) is applied s.c. every second day at a dose of 250 μg. IFN-β-1b is also used in cases of secondary-chronic progressive MS (SP-MS) with superimposed relapse activity.

Beta-IFNs take effect through various mechanisms [36–38]. Clinical effects with respect to MS include the inhibition of T cell proliferation, increase in the suppressor T cell activity, inhibition of proinflammatory cytokines such as TNF-α and IFN-γ, induction of immunomodulatory cytokines IL-10 and TGF-β, reduced expression of human leucocyte antigen (HLA) class II and adhesion molecules and the blockade of metal-proteinases and chemokines and reduced blood–brain-barrier permeability. Class I IFNs (alpha- and beta-interferons) act as secreted ligands at specific cell-surface receptors and lead to the transcription of genes that have anti-viral, anti-microbial, anti-proliferative/anti-tumorous and immunomodulatory effects [36]. Despite the development of leucocytopenia in the majority of patients, severe infections are rare during this therapy. At the injection site, local infections and even the formation of abscesses have been described (for details see Table 1).

Glatiramer acetate (Copaxone®) is given subcutaneously every day at a dose of 20 mg as a basic therapy for RR-MS and CIS. It is a mixture of synthesized polypeptides with an immunomodulating effect. The chemical structures are similar to myelin basic protein (MBP), a main component of the myelin layer. Glatiramer acetate binds various HLA haplotypes of antigen-presenting cells (APCs) [39]. During treatment a shift from T helper type 1 (Th1) to Th2 cells occurs, whereby the more active Th2 cells pass the blood–brain barrier. This Th1/Th2 shift leads to an increased production of anti-inflammatory cytokines such as IL-4, IL-6, IL-10 and neurotrophic factors, e.g. brain-derived neurotrophic factor (BDNF) [40]. Conversely, the release of proinflammatory cytokines such as IL-12 is reduced. Glatiramer acetate additionally promotes regulatory $CD8^+$ cells and, via the activation of the transcription factor forkhead box protein 3 (FoxP3), the conversion of conventional $CD4^+CD25^-$ T cells to regulatory $CD4^+CD25^+$ T cells [41].

In some cases changes in blood cell count have been observed, including leucocytosis as well as leucocytopenia, but also abnormal lymphocytic morphologies.

In the Phase III trial for glatiramer acetate [42], local reactions at the injection site were noted. Mild erythema and induration were the most commonly recognized adverse event (at least once during 730 days of treatment in 90% of treated patients and in 59% of the placebo arm). Inflammation as a sign of infectious complications was observed in 27·2% of the verum-treated patients *versus* 6·35% in placebo-treated participants. Similarly, in the follow-up study [43] local injection site reactions were common (66% glatiramer acetate *versus* 37% placebo). Skin reactions were mild, short-lived and not necessarily of infectious character. Skin necrosis was observed in none of the treated subjects.

In summary, basic therapies for MS (IFN-β-1b and -1b and glatiramer acetate), are safe with respect to infectious side effects [22,44,45]. Apart from local infections and rare abscess formation in the context of subcutaneous or intramuscular applications, no increased systemic risk of infection is found.

Oral MS treatment options ('orals')

Fingolimod (0·5 mg once daily, Gilenya®) is the first specific oral therapeutic agent for MS and is licensed as a first-line therapy in the United States according to the Food and Drug Administration (FDA), and as a second-line therapy for RR-MS in Europe according to the Eurpean Medicines Agency (EMA). After *in-vivo* phosphorylation fingolimod-phosphate, the active metabolite, modulates lymphocyte migration. As a functional antagonist of the S1P receptors on lymphocytes [46], fingolimod-phosphate blocks the migration of lymphocytes from the lymphatic tissues ('lymphocyte egress'). Because of its lipophilic characteristics it can also pass the blood–brain barrier, so that it can bind to S1P receptors on neural and neuroglial cells. After *in-vitro* investigations, this is a possible additional factor for the disease-modulating effect of fingolimod in the context of MS [47].

In the fingolimod licensing studies [48,49], acute infections of the lower respiratory tract appeared more frequently in the fingolimod group compared to the placebo

group. Severe infections were found in up to 2·6% of the patients, including a fatal case of herpes simplex (HSV) encephalitis and a fatal case of disseminated varicella zoster virus (VZV) infection. Therefore, patients who are negative for VZV antibodies should be vaccinated against VZV before treatment with fingolimod [50].

BG-12 or dimethyl-fumarate (Tecfidera®) is a further oral MS therapeutic agent which was approved in March 2013 by both the EMA and the FDA on the basis of the results of the Phase III studies, DEFINE [51] and CONFIRM [52,53]. At present, it is used in the United States as a basic therapeutic agent (240 mg b.i.d.) [54]. In the European Union (EU) legal licensing questions currently prevent the immediate introduction to the market.

Fumaric acid esters (Fumaderm®) have been licensed in Germany since 1994 for the treatment of psoriasis vulgaris [55]. Experimental data showed an anti-inflammatory as well as a cytoprotective effect that is driven mainly by the activation of the transcription factor Nrf-2 (nuclear factor erythroid-derived 2-related factor). Nrf-2 up-regulates various anti-oxidative signal pathways, leading to increased glutathione levels and inhibition of the translocation factor NF-κB into the cell nucleus. This brings about a reduced expression of the NF-κB dependent genes that regulate the expression of a cascade of inflammatory cytokines, chemokines and adhesion molecules [56]. In a Phase II study for testing BG-12 in the treatment of RR-MS, a significant reduction of disease activity was shown in magnetic resonance imaging (MRI) [57].

In the placebo-controlled Phase III study (DEFINE) [51] with 240 mg BG-12 administered twice or three times daily *versus* placebo, a significant reduction of the number of patients with relapse occurrences, annual relapse rates, illness progression rates and MRI lesions were described. Across the three study arms, this trial [51] showed a comparable incidence of infections (placebo 65%, BG-12 2×240 mg/day 64%, BG-12 3×240 mg/day 68%). Those observed most frequently were rhinopharyngitis, infections of the upper respiratory tract, infections of the urinary tract and influenza. Serious infections occurred in approximately 2% of all groups. Opportunistic infections were not registered. For patients with lymphocyte counts below $0{\cdot}5 \times 10^9$/l, no serious infections were found.

Another Phase III study (CONFIRM) [52] compared two BG-12 dosages with placebo and glatiramer acetate (reference arm). Compared with the placebo, BG-12 (both dosages) and glatiramer acetate reduced the rates of relapse and improved the neuroradiological outcome parameters significantly.

During the CONFIRM study [52], treatment infections in both study arms of BG-12 were detected in 56% of cases, comparable to infections in 50% of the cases treated with glatiramer acetate or placebo. Reported infections covered rhinopharyngitis, infections of the urinary tract, the upper airways, bronchitis, sinusitis and gastroenteritis. The frequency of serious infections was similarly low (1–2%) across all of the groups. Opportunistic infections were not observed.

Summarizing, the published clinical studies were thus in agreement on the fact that there is no increased risk of serious infections and there is no indication to date of opportunistic infections under BG-12.

On the basis of the currently available data [51,52], relevant side effects for BG-12 are primarily reddening of the skin (flushing), gastrointestinal symptoms (diarrhoea, nausea and upper abdominal pains), reduced counts of lymphocytes and increased liver values. However, there are some reports of cases of progressive multi-focal leucoencephalopathy (PML) and other side effects (in five cases) following the treatment of psoriasis with fumaric acid esters (available in Germany under the trade name Fumaderm®), as well as in other formulations [58–61]. In some cases the patients had been treated with fumaric acid for many years and developed distinctive leucocytopenias and lymphopenia. In some cases they also had further established risk factors for the development of PML, so the final causal proof is still lacking.

Teriflunomide (Aubagio®), an orally available dihydroorotate dehydrogenase inhibitor, blocks the pyrimidine synthesis [62] and was licensed by the FDA in 2012 [63] for first-line treatment of RR-MS. Licensing was supported by the EMA in March 2013 [64] and is expected to be available in Europe by the end of 2013. The regular dosage is 14 mg per day. Teriflunomide is the active metabolite of leflunomide (Arava®), which has already been used for many years in the treatment of rheumatoid arthritis. The mechanism of action is based on the effects on the *de-novo* pyrimidine synthesis in rapidly proliferating cells, which leads to blocking of the activation and proliferation of T and B lymphocytes. Slowly dividing or dormant cells remain largely uninfluenced, as these achieve pyrimidine synthesis by means of an alternative metabolic pathway (the salvage pathway) [62].

In the Phase III study (Teriflunomide Multiple Sclerosis Oral: TEMSO) [65] the annual relapse rate was reduced significantly compared to the placebo group, both with the 7 mg and 14 mg daily dosages. The higher dose also led to a significant reduction of the MRI T2 lesion volume and prolonged the time to a confirmed progression of disease. The time to the next relapse was increased significantly in both verum groups. All in all, teriflunomide was well tolerated and only a minority of the patients experienced serious side effects. The main side effects were diarrhoea, increases in alanine aminotransferase (ALAT), nausea and loss of hair or thinning-out. Among those side effects with an incidence above 10%, influenza infections were documented in 9·2 and 12% of the teriflunomide groups and in 10% of the placebo group. Urinary tract infections were documented in 7·3 and 10·3% of the teriflunomide groups and in 9·7% of the placebo group.

In all three arms of the study the frequency of serious infections was comparable (placebo 2·2%, teriflunomide 7 mg 1·6% and teriflunomide 14 mg 2·5%), among them three cases of pyelonephritis in the 14 mg teriflunomide group and one case of serious herpes zoster infection in the placebo group. Opportunistic infections were not observed.

The recently presented main findings of another major Phase III study (Teriflunomide Oral in people With relapsing multiplE sclerosis: TOWER) show similar effects to the TEMSO study with regard to effectiveness: both 7 and 14 mg of teriflunomide per day reduced the annual rate of relapse significantly compared with placebo. The higher dose led to a statistically significant reduction in the risk of a confirmed progression of disease by 31·5% compared to placebo [66].

Long-term data from the original Phase II study [67] with up to 8·5 years of follow-up [68] showed no new infection-related risks. The majority of infections were again of the upper respiratory tract and rhinopharyngitis. Influenza and infections of the urinary tract were also frequently reported. Serious adverse events (SAEs) included individual cases of appendicitis, bronchitis, pneumonia and infections of the urinary tract. So far, neither a progressive multi-focal leucoencephalopathy (PML) nor any other opportunistic infections have been observed and none of the infection-related complications led to discontinuation of the teriflunomide therapy [68].

In future, laquinimod will possibly be available as a further oral therapeutic option for treatment of RR-MS. In the previous studies, dosages of 0·3–0·6 mg/day were used. Future investigations will have to provide information on its suitability as a basic therapeutic application in the sense of a monotherapy or, when indicated, as a combined therapy with established basic therapeutic applications.

This 'small molecule' (a quinoline-3-carboxamide derivative) is an immunomodulator with both, anti-inflammatory and neuroprotective properties. It passes the blood–brain barrier irrespective of a disturbed function and accumulates in relevant concentrations in the brain, the spinal cord and in cerebrospinal fluid. In preclinical studies, significant effects on fundamental MS characteristic pathogenic mechanisms, such as inflammatory processes, myelin decomposition and axon loss have been shown [69]. It is assumed that this is due to a new and multi-dimensional mechanism with immunomodulating and neuroprotective potency independent of endogenous IFN-β. Experimental data from the experimental autoimmune encephalomyelitis (EAE) animal model of MS show histopathologically a reduction of macrophage and $CD4^+$ T cell infiltration, demyelinization and acute axonal damage. In addition to this, a shift of the cytokine balance – in favour of an anti-inflammatory Th2 profile – is detectable [70]. Other *in-vitro* data point to a laquinimod-dependent modulation of the NF-κB signal pathway [71].

Using dosages of 0·3 and 0·6 mg/day the numbers of new gadolinium-enhancing MRI lesions were decreased significantly in two Phase IIa and IIb studies [72,73]. No relevant infection-related problems were reported. Laquinimod at 0·6 mg per day slowed down the disease progression, lowered the annual relapse rate and reduced the cumulative number of gadolinium-enhancing and new or growing T2-MRI lesions significantly compared with the placebo in a Phase III study (Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis: ALLEGRO) [74].

The second Phase III study (Benefit–Risk Assessment of Avonex and Laquinimod: BRAVO) [75] investigates the effectiveness of 0·6 mg of laquinimod compared with placebo and the active comparator IFN-β-1a i.m.

In the previous placebo-controlled studies [72–74,76] using laquinimod an increased number of infections of the respiratory tract were found (ALLEGRO: 7·5 *versus* 4·5%) as well as individual cases of herpes simplex and herpes zoster infections, although these were self-limiting and remained restricted to the skin. At present there is no indication that serious or life-threatening infections are caused by the therapy.

Biologicals

Monoclonal antibodies

Monoclonal antibodies (mAb) used as disease-modifying drugs (DMD) in MS interfere selectively with the immune response by modulating immune-cell functions, e.g. blocking of cell adhesion or of the antigen-specific immune-cell depletion [77,78]. Currently, in the treatment of MS, natalizumab [anti-very late antigen-4 antibody (VLA-4-antibody)] and on an off-label use basis rituximab (anti-CD-20-antibody) are used [79]. At present, US and European authorities are evaluating the licensing of alemtuzumab (anti-CD52-antibody), another mAb which has also already been in use for many years on an off-label use basis to treat MS [80,81].

Further monoclonal antibodies for the treatment of MS, such as ocrelizumab [82–84] and ofatumumab [85,86] (anti-CD-20-antibodies), are currently tested in clinical studies [77,87].

Receptor-blocking monoclonal antibodies

Natalizumab (Tysabri®) is a humanized monoclonal immunoglobulin (Ig)G4 antibody that unfolds its main effect via alpha-4-integrin inhibition and thereby reduces the migration of VLA-4-positive lymphocytes to the central nervous system (CNS) [88]. The treatment consists of 300 mg of natalizumab intravenously (i.v.) every 4 weeks and is currently applied as a second-line therapy for RR-MS, and may also be used as a first-line therapy in rapidly advancing RR-MS.

Those undergoing therapy in the relevant trials experience a reduction in the annual rate of relapse of 68% compared with placebo and 55% compared with IFN-β-1a [89–91]. After 24 weeks, MS progression is reduced by 54% in comparison to placebo and 18% in comparison to IFN-β-1a [89–91]. Adverse effects such as allergic and post-infusion reactions and the formation of neutralizing antibodies against the substance were described. Under certain circumstances, progressive multi-focal leucoencephalopathy (PML) can appear in the context of natalizumab treatment. This is a serious illness that normally leads to severe disability or illness resulting in death. A causal therapy of JC virus infection does not, as yet, exist [92]. First-line strategy in natalizumab-associated JC virus infection is elimination of the therapeutic antibody by plasmapheresis. However, plasmapheresis may cause an inflammatory immunological reconstitution syndrome (IRIS) with paradoxical worsening of the neurological findings [93], which can make steroid pulse therapy, or even intensive medical care of the patient, necessary. Other options to treat PML with a low level of evidence are application of mefloquine [94] or mirtazapine [95–97]. Both options are under further investigation in clinical trials. The risk for PML increases with positive JC antibody findings; after a treatment period of 2 years and with a prior immunosuppressive therapy [98,99], if all three risk factors are present 11 of 1000 patients are estimated to develop PML, making it crucial to weight the risks and benefits of continuing treatment in these situations [100]. Close monitoring of warning signs and patient education are essential for the early detection of PML.

In the licensing-relevant studies, there were frequent reports of infections of the urinary tract and of rhinopharyngitis, while only one case of cryptosporidium-associated diarrhoea and of fatal herpes encephalitis was observed. In comparison to placebo, patients with natalizumab monotherapy seemed to have only a slightly increased risk of developing side effects, with 21 *versus* 17% urinary tract infections, 17 *versus* 16% lower respiratory tract infections, 11 *versus* 9% gastroenteritis, 9 *versus* 7% tooth infections, 8 *versus* 7% herpes and 7 *versus* 5% tonsillitis, respectively [100].

Cell-depleting monoclonal antibodies

Alemtuzumab (Lemtrada®) is a humanized antibody (IgG1k) that is directed against CD 52 and leads to long-lasting changes in the adaptive immune system by depletion of B and T lymphocytes [101–103]. The treatment is administered in annual therapeutic cycles. Initially, 12 mg of alemtuzumab are infused on each of 5 consecutive days. After 12 months a further three such infusions are given.

Two Phase III studies [104,105] show highly promising results: alemtuzumab reduces the relapse rate both in patients who have not previously been given immunomodulatory treatment (CARE-MS I) and in patients who show disease activity despite a standard basic therapy (CARE-MS II).

The efficacy of this therapy accompanies controllable infusion-associated side effects, infections and particularly with the development of autoimmune diseases affecting the thyroid gland or leading to immune thrombocytopenias, requiring intensive follow-up.

During the Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS I) study [104,105], infections appeared more frequently under alemtuzumab than under IFN-β-1a. Of these infections, 98% were mild to moderate and none of the infections led to discontinuation of the therapy. The infections affected mainly the upper respiratory tract, the urinary tract and herpes infections. None of the infections were life-threatening or fatal. One patient from an endemic region developed tuberculosis under alemtuzumab, which was treated using standard therapy.

The CARE-MS II study [104,105] revealed more cases of infection under alemtuzumab compared to IFN-β-1a (77 *versus* 66%). The most frequent of these infections were rhinopharyngitis (29 *versus* 24%), urinary tract infections (21 *versus* 11%) and infections of the upper respiratory tract (16 *versus* 12%). Severe infections occurred in 4 and 1% of the treated patients, respectively, among them mucocutaneous herpes simplex, candidiasis and herpes zoster infections requiring in-patient treatment. In both the CARE-MS I and CARE-MS II studies, prophylactic use of aciclovir resulted in a reduced number of patients with herpes virus infections compared to patients without prophylactic treatment (CARE-MS I: 1 *versus* 3%; CARE-MS II: 0·5 *versus* 2·8% after first alemtuzumab application and 0·4 *versus* 2·1% after the second alemtuzumab application). One patient from an endemic region developed tuberculosis during alemtuzumab high-dose treatment, resulting in termination of the treatment. One other patient had to be treated due to a positive tuberculin skin test. Both patients responded to anti-tuberculosis drugs.

According to a current press release, the EMA has authorized the use of alemtuzumab in the treatment of adult patients with RR-MS who have clinically or MR-image morphologically defined illness activity [106].

Rituximab (MabThera®) is a chimeric monoclonal antibody directed against CD20-expressed B precursor cells and B lymphocytes that results in the depletion of these target cells [77].

In a Phase II study [107] a single course of rituximab reduced the number of inflammatory brain lesions shown in the MRI and the rate of relapses over a period of 48 weeks, compared to placebo. So far, rituximab has not been investigated in a Phase III study.

Serious infection-related complications of this therapy include new manifestations, reactivation or worsening of viral disease such as the reactivation of hepatitis B or JC virus infections (PML) [108,109]. In a study of primary progressive MS [110], 4·5% of the patients treated with

rituximab were found to have severe infections compared to <1·0% in the placebo group.

Daclizumab is a humanized mAB which binds specifically to the IL-2Rα receptor (CD25). It is used to prevent kidney transplant rejection. Several Phase II studies showed a significant reduction in gadolinium-enhancing MRI lesions and clinical disability in MS [111–114]. The clinical effects of daclizumab on MS are thought to be associated with the propagation and activation of immunoregulatory CD56 (bright) NK cells, which kill activated autologous T cells and thereby regulate the adaptive immune system [111,114]. However, daclizumab also blocks the presentation of IL-2 by mature dendritic cells to T cells and thus inhibits antigen-specific T cells [112]. Apart from this, daclizumab appears to influence the development of lymphoid cells [112].

The daclizumab in active relapsing multiple sclerosis (CHOICE) study [114], a double-blind, randomized Phase II study, investigated daclizumab as an add-on therapy to IFN-β. The combined therapy reduced the number of new or gadolinium-enhancing MRI lesions compared to IFN-β monotherapy.

The existing safety data do not reveal any relevant infection-related side effects of daclizumab. In the CHOICE study [114,115], the most frequent serious adverse events (AEs) were infections (7% under daclizumab/IFN *versus* 3% under placebo/IFN). Serious adverse events were reported for 13% of the patients treated with daclizumab compared with 5% in the control group. Of these, infections were the most frequent causes (5% under daclizumab/IFN *versus* 1% under placebo/IFN). Overall, there were no opportunistic infections or fatalities related to infections.

In the recently published daclizumab high-yield process in relapsing–remitting multiple sclerosis (SELECT) placebo-controlled trial [116], investigating 621 patients, daclizumab high-yield process (HYP) dosages of 150 or 300 mg every 4 weeks s.c. are used. The study showed a significant reduction in the relapse rate and an increase in the number of relapse-free patients during the 12-month treatment period lasting a year in both dosages. Serious adverse events were more frequent in the placebo group. Severe infection-related complications appeared in 2% of the patients receiving daclizumab, none receiving placebo. For six of seven patients the therapy could be continued after the infection had subsided. Oral herpes infections occurred in 5–6% of the patients in all three groups. In each group one case of herpes zoster was observed. In all, four malignancies were diagnosed: one cervix carcinoma (placebo/150 mg daclizumab) and two malignant melanomas (300 mg daclizumab).

At present, alongside the Phase II studies (SELECT[117]/SELECTION [118]) there is a Phase III study programme (DECIDE[119]/OBSERVE[120]/EXTEND [121]) to test daclizumab in MS as a monotherapy in comparison to IFN-β-1a.

In summary, the newer treatment options (monoclonal antibodies, orals) appear to require individual safety assessments. To some extent the increased infection-related risks will only be recognizable after completion of the licensing-relevant clinical studies, and will make special vigilance and comprehensive clarification, plus intensive multi-disciplined medical care of the patients, necessary [122].

Intravenous immunoglobulins (IVIgs) unfold their immunomodulating effect via a variety of mechanisms, such as inhibition of the complement system, influence on B cells and autoantibodies, macrophages and T cells, and modulation of cytokine networks [123].

Given the currently available clinical study data and the availability of alternatives, in multiple sclerosis they currently constitute a reserve preparation only; for example, when other therapeutic options are contraindicated, as in cases of pregnancy and lactation [124]. Typical dosages for these individual cases are between 0·15–0·4 g/kg body weight per month.

Despite extensive and modern safety measures in the manufacturing process and in the choice of blood donors, IVIg, as biological products, have a small residual risk for the transfer of infectious agents such as uncoated viruses or prions [125].

Cytostatic agents

Cytostatic agents for the treatment of MS are allocated to various effective groups, as follows.

1 Anti-metabolites such as azathioprine (e.g. Imuran®) influence, among other things, T- and B-cell proliferation and thereby the cellular and humoral immune response [16].
2 Cyclophosphamide (e.g. Cytoxan®) exerts its effect on the DNA synthesis (cross-links) via its alkylating metabolites and results in single- and double-strand breaks in rapidly proliferating cells. As a consequence, there is an increase in $CD8^+$-suppressor cells and a reduction in $CD4^+$-helper cells [126].
3 By intercalation, mitoxantrone (e.g. Novantrone®/Ralenova®) causes cross-linkage and strand breaks of the DNA. Mitoxantrone also obstructs the transcription of RNA and inhibits topoisomerase II, which is responsible for the uncoiling and repair of damaged RNA. It operates independently of the cell cycle. Its anti-proliferative effect on B and T lymphocytes, as well as macrophages, reduces MS disease progression [127].

Immunosuppressive agents are applied in MS in cases of escalation therapy or as reserve therapeutics [128].

Generally speaking, the use of classical immunosuppressive agents is connected to an increased risk of infection. For this, the presence of latent infections or pathological

changes in cellular and humoral immune parameters must be assessed prior to treatment and, if necessary, infections must be treated fully in advance [129]. Basically, in the context of long-term therapy, an increased clinical and paraclinical vigilance regarding infection-related complications is necessary (Tables 1 and 2).

Summary

With an increasing number of modern compounds, more potent MS treatment options are available. However, increased efficacy seems to accompany a new and more specific spectrum of side effects, including infectious aspects. On one hand, this is due to more specific mechanisms of action; on the other hand, it is also certainly a result of closer monitoring and reporting in clinical trials. Despite the comparatively low number of infections overall, some of these are serious and occasionally even fatal. The latter is unacceptable for relatively young patients suffering from a chronic but not life-threatening disease. Control of side effects and minimizing treatment-associated risks will be one of the future challenges in MS treatment. To facilitate this, long-term monitoring and reporting in treatment registries will have to play a major role. Patient-focused treatment stratification will be another relevant issue (Box 1).

According to current knowledge for the new oral treatment options, which are awaited eagerly by many patients, no fundamental new infectious complications are relevant and their use appears to be safe with respect to infectious aspects.

Box 1. Summary of major findings

- Relapse treatment (GCS/plasmapheresis) requires awareness and individual management of potential infectious risks
- Long-term established DMDs are safe with regards to infectious complications, if used in the correct manner
- New oral multiple sclerosis (MS) therapies might cause infectious problems due to their mechanism of action; latent or chronic infections and the individual vaccination status should be considered carefully before initiating treatment
- Use of immunosuppressive drugs goes along with higher risks of infection; absence of relevant infection before treatment initiation and follow-up monitoring during treatment is recommended
- Use of biologicals such as monoclonal antibodies (mAb) can lead to relevant infectious complications; to avoid fatal outcome of treatment intensive and long-lasting monitoring and multi-disciplinary surveillance is mandatory

Author contributions

A. W. and U. Z. designed the research; A. W. and M. L. performed the literature search and data extraction. All authors analysed the data, A. W and M. L. wrote the paper, M. L., U. Z. and E. R. reviewed and provided comments on the manuscript.

Disclosures

The corresponding authors declare the following potential conflicts of interest: U. K. Z. is on the speaker's list of Bayer Health Care, Biogen Idec, Merck Serono and Aventis/Teva. E. C. R. received speaker's honoraria and travel expense compensation from Sanofi Pasteur MSD, GlaxoSmithKline, Novartis Vaccines, Roche Pharma and Bayer. A. W. received speaker's honoraria and travel expense compensation from Schering, Bayer Health Care, Octapharma AG, Novartis, Biogen, Genzyme and Merck Serono. M. L. received speaker's honoraria or travel expense compensation from Abbvie, Novartis Vaccines, Gilead, Janssen Cilag and Roche Pharma.

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