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Review

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Cutaneous adverse events associated with disease-modifying treatment in multiple sclerosis: a systematic review

Deepak MW Balak[1], Gerald JD Hengstman[2,3], Aysun Çakmak[4] and H Bing Thio[1]

Abstract

Glatiramer acetate and interferon-beta are approved first-line disease-modifying treatments (DMTs) for multiple sclerosis (MS). DMTs can be associated with cutaneous adverse events, which may influence treatment adherence and patient quality of life. In this systematic review, we aimed to provide an overview of the clinical spectrum and the incidence of skin reactions associated with DMTs. A systematic literature search was performed up to May 2011 in Medline, Embase, and Cochrane databases without applying restrictions in study design, language, or publishing date. Eligible for inclusion were articles describing any skin reaction related to DMTs in MS patients. Selection of articles and data extraction were performed by two authors independently. One hundred and six articles were included, of which 41 (39%) were randomized controlled trials or cohort studies reporting incidences of mainly local injection-site reactions. A large number of patients had experienced some form of localized injection-site reaction: up to 90% for those using subcutaneous formulations and up to 33% for those using an intramuscular formulation. Sixty-five case-reports involving 106 MS patients described a wide spectrum of cutaneous adverse events, the most frequently reported being lipoatrophy, cutaneous necrosis and ulcers, and various immune-mediated inflammatory skin diseases. DMTs for MS are frequently associated with local injection-site reactions and a wide spectrum of generalized cutaneous adverse events, in particular, the subcutaneous formulations. Although some of the skin reactions may be severe and persistent, most of them are mild and do not require cessation of DMT.

Keywords

Interferon-beta, glatiramer acetate, skin reactions, adverse events, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system, which is characterized by infiltration of immune cells, loss of myelin and axons, and formation of multifocal plaques in the brain and the spinal cord.[1] MS is a common disease, with approximately 2.5 million people affected worldwide, most of whom are young and middle-aged adults.[2] At present, a definitive cure for MS is lacking so that its treatment is aimed primarily at reducing symptoms and disease progression via modulation of the immune system.[3]

To date, approved first-line disease-modifying therapies (DMTs) for the treatment of MS include glatiramer acetate (GA) and two types of interferon-beta (IFN-β): IFN-β-1a and IFN-β-1b. Both GA and IFN-β are assumed to affect multiple immunological processes, but the exact mechanisms underlying their beneficial effects in MS are not fully understood.[4,5] GA and IFN-β require administration via subcutaneous (SC) injections, while IFN-β-1a is also

[1]Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands.
[2]Department of Neurology, Catharina Ziekenhuis, Eindhoven, The Netherlands.
[3]Regionaal MS Centrum Oost-Brabant, Eindhoven, The Netherlands.
[4]Department of Neurology, Amphia Ziekenhuis, The Netherlands.

Corresponding author:
HB Thio, Department of Dermatology, Erasmus Medical Center, Burg's Jacobsplein 51, 3015 CA Rotterdam, The Netherlands.
Email: h.thio@erasmusmc.nl

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available as an intramuscular (IM) formulation. The dosage and frequency of administration differ between the four DMTs: GA is injected once daily, IFN-β-1b once every other day, SC IFN-β-1a three times a week, and IM IFN-β-1a once a week.

GA and IFN-β have proven albeit partial efficacy in reducing the frequency of relapses and disease activity, as shown by magnetic resonance imaging.[6,7] Both therapies are generally safe and well-tolerated with an acceptable side-effect profile. However, patients treated with DMTs may frequently experience cutaneous adverse events.[8] These cutaneous side-effects may include local injection-site reactions, such as erythema, induration, swelling, haemorrhage, pain, and pruritus around injection sites.[9,10] Next to these usually transient injection-site reactions, more severe and persisting cutaneous complications to DMTs may occur, such as lipoatrophy and skin necrosis and ulcers.[11,12] Cutaneous adverse events to DMTs can have important clinical implications as they may be associated with reduced treatment adherence and quality of life.

The aim of this systematic review is to provide an overview of the frequency and the spectrum of cutaneous adverse reactions associated with DMTs in MS patients.

Methods

Definitions

Adverse cutaneous events to DMTs were defined as any localized or generalized abnormality involving the skin during the treatment, regardless of the assumed causality with the drug. DMTs included SC glatiramer acetate (Copaxone®, Sanofi Aventis and Teva), SC IFN-β-1a (Rebif®, Merck Serono), IM IFN-β-1a (Avonex®, Biogen Idec), and SC IFN-β-1b (Betaferon® and Betaseron®, Bayer Schering).

Search strategy and selection criteria

An electronic literature search was performed up to 21 May 2011 in the MEDLINE, EMBASE, and Cochrane databases, including the Cochrane Multiple Sclerosis Group Trials Register, using combinations of the following keywords and/or medical subject headings (MeSH): 'glatiramer acetate', 'interferon-beta', 'multiple sclerosis', 'cutaneous reaction', 'skin', 'dermatology' and 'adverse event' (Supplement 1). We also included randomized controlled trials (RCTs) assessing the efficacy and safety of DMTs, considering that some of these trials may have had reported cutaneous adverse events as secondary or safety outcomes. Additional relevant articles were selected by screening the reference lists of included articles. Also, the manufacturers of GA and the IFN-β preparations were contacted for additional references.

Two authors (DMWB, AC) independently assessed the articles for eligibility for inclusion. Differences between the authors were resolved by a consensus agreement. Articles were first screened for relevance according to the title and the abstract. The remaining articles were then full-text assessed. Eligible for inclusion were articles describing any skin reaction or other dermatological symptom during treatment with one of the DMTs. Articles were excluded if they described diseases other than MS, if they did not describe adverse cutaneous events, or if they described medications other than GA or IFN-β. No limitations in language, study design, or study date were applied. Data were extracted from the included articles independently by two authors (DMWB, AC).

Results

Literature search

Our literature search yielded 1092 articles that were screened for eligibility, of which 106 articles were included (Supplement 2). There were two cross-sectional studies reporting the prevalence of cutaneous adverse events during DMT treatment. Thirty-nine (37%) of the included articles were RCTs or prospective follow-up studies that described general incidences of localized skin reactions to DMTs (Table 1). The other included articles (61%) were mostly case reports and case series that reported a total of 106 patients with a variety of localized and generalized cutaneous adverse events to DMTs (Table 2 and Table 3).

Local injection-site reactions

Incidences of local injection-site reactions were reported in most RCTs, but a majority of these trials used different definitions or did not specify their definition of local injection-site reactions. The used definitions of injection-site reaction in these trials included redness or erythema, swelling, pain, pruritus, bruising, irritation, inflammation, or induration of the skin around an injection site. In some of the RCTs, severity of the injection-site reactions was graded as mild, moderate, or severe. Also, some trials mentioned incidences of other cutaneous events, such as skin rash, cutaneous necrosis, and lipoatrophy. In only a few RCTs, adverse skin reactions were a primary outcome.[52–55]

Table 1 gives an overview of the reported proportions of patients with injection-site reactions during DMT treatment. The RCTs are heterogeneous in their applied definition of skin reactions, sample size, follow-up duration and the used dosage or frequency of the DMT, among others, making it difficult to compare directly the incidences of injection-site reactions. Injection-site reactions developed in 2–33% of patients using IM IFN-β-1a. The proportion of patients with injection-site reactions for SC IFN-β-1a was between 13% and 89%, while about 22– 96% of SC

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Table 1. Summary of studies describing incidence or prevalence of cutaneous adverse events associated with glatiramer acetate and interferon-beta treatment for multiple sclerosis.

Study	Type of study	Number of patients	Follow-up duration	Treatment	Incidence of cutaneous adverse events	Cutaneous adverse events
Mikol et al (2008)[13]	Randomized open-label study	378	1.8 years	GA 20 mg daily	7–30%	Injection-site reactions*
Meca-Lallana et al (2010)[14]	Follow-up study	28	1–1.5 years	GA 20 mg daily	21%	Injection-site reactions
Wolinsky et al (2007)[15]	RCT	627	3 years	GA 20 mg daily	9–57%	Injection-site reactions
Johnson et al (1995)[16]	RCT	125	2 years	GA 20 mg daily	19–64%	Injection-site reactions
Korczyn et al (1996)[17]	Database of multiple RCT data	857	—	GA (different dosages)	14–54%	Injection-site reactions
Zwibel (2006)[18]	Open-label study	805	3.5 years	GA 20 mg daily	54%	Injection-site reactions
Comi et al (2011)[19]	RCT	586	1 year	GA 20 mg daily	56%	Injection-site reactions
		569		GA 40 mg daily	58%	Injection-site reactions
Miller et al (2008)[20]	Open-label study	46	12 years	GA 20 mg daily	≥ 50%	Injection-site reactions Lipoatrophy (n=4)
O'Connor et al (2009)[21]	Phase III RCT	445	2–3.5 years	GA 20 mg daily	58%	Injection-site reactions
Johnson et al (1998)[22]	Extension to RCT	125	2.5 years	GA 20 mg daily	66%	Injection-site reactions
Flechter et al (2002)[23]	Open-label study	38	2 years	GA 20 mg daily	70%	Injection-site reactions
				GA 20 mg eod	67%	Lipoatrophy (n=3 in daily group)
Flechter et al (2002)[24]	Open-label study	68	1-2 years	GA 20 mg eod	61%	Injection-site reactions
					7%	Rash
Debouverie et al (2007)[25]	Open-label study	205	4 years	GA 20 mg daily	81%	Injection-site reactions
Johnson et al (1995)[16]	RCT	125	2 years	GA 20 mg daily	90%	Injection-site reactions
European Study group on IFN-β-1b in secondary progressive MS (1998)[26]	RCT	360	2–3 years	IFN-β-1b 250 ug eod	5%	Necrosis;
					21%	Rash
					44%	Injection-site reactions;
					50%	Inflammation
Gottesman et al (2006)[27]	Open-label study	22	0.4 years	IFN-β-1b 500 ug eod	22%	Injection-site reactions Rash/urticaria (n=1)
Brochet et al (2006)[28]	RCT	294	0.1 years	IFN-β-1b (auto-injector)	24%	Injection-site reactions
				IFN-β-1b	36%	Injection-site reactions
Durelli et al (2002)[29]	RCT	94	2 years	IFN-β-1b 250 ug eod	37%	Injection-site reactions
Neilley et al (1996)[30]	Open label study	72	—	IFN-β-1b 500 ug eod	42%	Skin reactions
Kappos et al (2006)[31]	RCT	292	2 years	IFN-β-1b 250 ug eod	48%	Injection-site reactions
					11%	Rash
The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group (1996)[32]	RCT	124	3 years	IFN-β-1b 500 ug eod	46–66%	Injection-site reactions
					4%	Injection-site necrosis

(*Continued*)

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Table 1. (Continued)

Study	Type of study	Number of patients	Follow-up duration	Treatment	Incidence of cutaneous adverse events	Cutaneous adverse events
Hurwitz et al (2008)[33]	Randomised pilot study	33	0.2 years	IFN-β-1b 500 ug eod	58%	Injection-site reactions
		38		IFN-β-1b 250 ug eod	66%	Injection-site reactions Rash (6–11%)
O'Connor et al (2009)[21]	RCT	888	2–3.5 years	IFN-β-1b 250 ug eod	48%	Injection-site reactions
		887		IFN-β-1b 500 ug eod	55%	Injection-site reactions
Kappos et al (2009)[34]	Extension to RCT	468	5 years	IFN-β-1b 250 ug eod	54%	Injection-site reactions
Baum et al (2006)[13]	RCT	151	0.5 years	IFN-β-1b (with mannitol)	92%	Injection-site reactions
		145		IFN-β-1b (with glucose)	96%	Injection-site reactions
Rio et al (1998)[35]	Prospective follow-up study	95	1 year	IFN-β-1b 500 ug eod	70%	Skin reactions
Montalban et al (2009)[36]	RCT	36	2 years	IFN-β-1b 250 ug eod	78%	Injection-site reactions
Flechter et al (2002)[24]	Open-label study	20	2 years	IFN-β-1b 250 ug eod	80%	Injection-site reactions
Reder et al (2010)[37]	Cross-sectional follow-up study of RCT	69	—	IFN-β-1b 250 ug eod	81%	Injection-site reactions
Cohen et al (2010)[74]	RCT	431	1 year	IM IFN-β-1a 30 ug/week	0.5%	Basal-cell carcinoma Squamous-cell carcinoma
Jacobs et al (1996)[38]	RCT	158	2 years	IM IFN-β-1a 30 ug/week	2%	Injection-site reactions
Havrdova et al (2009)[39]	Extension to RCT	60	3 years	IM IFN-β-1a 30 ug.week	3%	Erythematous rash
Ghezzi et al (2007)[40]	Follow up study	52	1.8 years	IM IFN-β-1a 30 ug/week	4%	Injection-site reactions
Schwid et al (2005)[41]	Extension to RCT	223	0.6 years	IM IFN-β-1a 30 ug/week	33%	Injection-site reactions
		272		SC IFN-β-1a 44 ug TIW	51%	Injection-site reactions
Sandberg-Wollheim et al (2005)[42]	RCT	338	1.2 years	IM IFN-β-1a 30 ug/week	30%	Mild injection-site reactions (moderate 5%)
		339		SC IFN-β-1a 44 ug TIW	75%	Mild injection-site reactions (moderate 15%; severe 1%)
Herndon et al (2005)[43]	Extension to RCT	382	6 years	IM IFN-β-1a 30 ug/week	35%	Injection-site reactions
Durelli et al (2002)[29]	RCT	88	2 years	IM IFN-β-1a 30 ug/week	8%	Injection-site reactions
Leary et al (2003)[44]	RCT	15	2 years	IM IFN-β-1a 30 ug/week	7%	Injection-site reactions
				IM IFN-β-1a 60 ug/week	15%	Injection-site reactions
Panitch et al (2002)[45]	RCT	337	0.5 years	IM IFN-β-1a 30 ug/week	28%	Injection-site reactions
Phillips et al (2004)[46]	Open-label study	153	2 years	IM IFN-β-1a 30 ug/week	31%	Injection-site reactions
Giovannoni et al (2009)[14]	Open-label study	260	1.8 years	SC IFN-β-1a 44 ug TIW (Rebif new formulation)	31%	Injection-site reactions Rash (*n*=16)
Mikol et al (2008)[13]	Randomized open-label study	381	1.8 years	SC IFN-β-1a 44 ug TIW	41%	Injection-site reactions Rash (*n*=28)
Freedman et al (2005)[47]	RCT	87	0.9 years	SC IFN-β-1a 22 ug TIW	13%	Injection-site reactions
		88		SC IFN-β-1a 44 ug TIW	26%	Injection-site reactions

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Table 1. (Continued)

Study	Type of study	Number of patients	Follow-up duration	Treatment	Incidence of cutaneous adverse events	Cutaneous adverse events
Andersen et al (2004)[48]	RCT	186	3 years	SC IFN-β-1a 22 ug/week	31%	Injection-site reactions
Oger et al (2005)[49]	RCT	87	2 years	SC IFN-β-1a 22 ug TIW	66%	Injection-site reactions
		85		SC IFN-β-1a 44 ug TIW	66%	Abscess at injection site (*n*=1)
Panitch et al 2002[45]	RCT	339	0.5 years	SC IFN-β-1a 44 ug TIW	89%	Injection-site reactions Rash (*n*=56)
PRISMS study group (1998)[50]	RCT	189	2 years	SC IFN-β-1a 22 ug TIW	39%	Injection-site reactions
		184		SC IFN-β-1a 44 ug TIW	40%	Injection-site reactions
Devonshire et al (2010)[16]	Prospective follow-up study	102	0.2 years	SC IFN-β-1a 44 ug TIW (Rebiject II)	76%	Injection-site reactions
Gold et al (2005)[51]	RCT	189	4 years	SC IFN-β-1a 22 ug TIW	73%	Injection-site reactions (skin necrosis: *n*=7)
		184		SC IFN-β-1a 44 ug TIW	71%	Injection-site reactions (skin necrosis: *n*=13)
Lugaresi et al (2008)[15]	Prospective follow-up study	76	1 year	SC IFN-β-1a 44 ug TIW (Rebiject)	79%	Injection-site reactions (*n*=50 persisted)
Panitch et al (2002)[45]	RCT	339	0.5 years	SC IFN-β-1a 44 ug TIW	83%	Injection-site reactions

*Injection site reactions include erythema, swelling, oedema, pain, pruritus, bruising, haemorrhage, irritation, and induration.
Abbreviations: eod, every other day; GA, glatiramer acetate; IFN-β, interferon beta; IM, intramuscular; NA, not applicable; RCT, randomized controlled trial; RRMS, relapsing remitting multiple sclerosis; SC, subcutaneous; TIW, three times a week.

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Table 2. Case-reports and case-series describing cutaneous reactions to glatiramer acetate and interferon-beta treatment of multiple sclerosis.

Type of skin lesion	Total no. of case reports	Total no. of patients	Histology obtained (no. of patients)	DMT				Implications for treatment		
				GA	SC IFN-β-1a	IM IFN-β-1a	IFN-β-1b	Stopped	Continued	Unknown
Lipoatrophy	8	30	20	28	1	–	1	29	1	–
Cutaneous ulcers	4	20	20	–	–	–	20	4	2	14
Cutaneous necrosis	12	15	9	2	1	–	12	6	4	5
Panniculitis	4	5	5	–	2	–	3	2	3	–
Urticaria	3	4	0	–	–	3	1	4	–	–
Cutaneous vasculitis	4	4	3	1	2	–	2	4	–	–
Embolia cutis medicamentosa	4	4	3	3	1	–	–	–	3	1
Lupus-like reactions	2	3	3	–	–	–	3	1	–	2
Psoriasis	3	3	1	–	1	–	2	1	1	1
Allergic local reactions	1	3	0	3	–	–	–	1	2	–
Systemic L.E.	1	1	0	–	1	–	–	1	–	–
Cutaneous LE	1	1	0	–	–	1	–	1	–	–
Fixed drug eruption	1	1	1	–	–	–	1	1	–	–
L.E. profundus	1	1	1	–	–	–	1	1	–	–
Scleromyxedema	1	1	1	–	–	1	–	1	–	–
Cutaneous mucinoses	1	1	1	–	–	–	1	1	–	–
Granulomatous dermatitis	1	1	1	–	–	–	1	1	–	–
Cutaneous T cell lymphoma	1	1	1	1	–	–	–	–	1	–
Cutaneous T cell pseudolymphoma	1	1	1	1	–	–	–	–	1	–
Calcified noduli	1	1	1	–	1	–	–	–	1	–
Dermatomyositis	1	1	1	–	–	1	1	1	–	–
Subcutaneous infiltration	1	1	1	–	–	–	1	–	1	–
Erythema elevatum diutinum	1	1	1	–	1	–	–	1	–	–
Erythema nodosum	1	1	1	1	–	–	–	–	1	–
Nonscarring alopecia	1	1	0	1	–	–	–	1	–	–
Vitiligo	1	1	0	–	1	–	–	1	–	–

Abbreviations: DMT, disease-modifying therapy; GA, glatiramer acetate; IFN-β, interferon-beta; L.E., lupus erythematosus; SC, subcutaneous.

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Table 3. The spectrum of cutaneous adverse reactions associated with the different disease-modifying treatments .

SC glatiramer acetate	SC IFN-β-1a	IM IFN-β-1a	SC IFN-β-1b
Lipoatrophy	Lipoatrophy	Cutaneous SLE	Lipoatrophy
Cutaneous necrosis	Cutaneous necrosis	Urticaria	Cutaneous ulcers
Panniculitis	Panniculitis	Drug eruption	Cutaneous necrosis
Cutaneous vasculitis	Cutaneous vasculitis	LEP	Panniculitis
Embolia cutis medicamentosa	Embolia cutis medicamentosa	Scleromyxedema	Cutaneous vasculitis
Cutaneous T cell lymphoma	Psoriasis		Cutaneous SLE/LEP
Cutaneous T cell pseudolymphoma	Calcified noduli		Lupus-like reactions
Erythema nodosum	Dermatomyositis		Psoriasis
Alopecia	Erythema elevatum diutinum		Granulomatous dermatitis
	Vitiligo		Subcutaneous infiltration
			Fixed drug eruption

Abbreviations: SC, subcutaneous; IFN, interferon; IM, intramuscular; SLE, systemic lupus erythematosus; LEP, Lupus erythematosus profundus.

IFN-β-1b patients and 7–90% of GA patients had developed local injection-site reactions.

Lipoatrophy

Lipoatrophy was a frequently reported adverse skin reaction, mostly in patients treated with GA. A prospective follow-up study reported that 4 (15%) out of 27 patients treated with GA had developed localized lipoatrophy at sites of injection after 3 years of treatment.[12] A larger, cross-sectional study from a single outpatient MS clinic in Canada found that 45% (34 out of 76) of patients with GA therapy had developed lipoatrophy after, on average, 2.4 years of treatment.[56] Another Canadian study assessed 100 consecutive patients receiving MS treatment, and reported 9 (64%) out of 14 patients treated with GA who had developed lipoatrophy.[57]

There were multiple case reports and case series describing a total of 30 patients who developed lipoatrophy several years after initiation of GA (Table 2). In some of these cases, lipoatrophy persisted or continued to enlarge despite cessation of GA.[58,59] There were two documented cases published in which lipoatrophy was associated with SC IFN-β-1a and IFN-β-1b, respectively.[60,61] Some case reports reported a combination of panniculitis and lipoatrophy in association with GA or with IFN-β-1b.[57,60,62]

Cutaneous ulcers and necrosis

Cutaneous ulcers were mainly described in patients who were treated with IFN-β-1b. A study by Webster and colleagues reported 8 (2%) out of 400 patients treated with IFN-β-1b who had developed skin ulcers.[63] Elgart and colleagues described 6 (6%) out of 100 consecutive patients on IFN-β-1b therapy with ulcers.[64]

In addition, several published case reports reported an association between IFN-β-1b therapy and the development of cutaneous ulcers and skin necrosis at multiple injection sites.[65–75] GA and SC IFN-β-1a have also been linked to skin ulcerations with skin necrosis at injection sites in two case reports.[75,76]

Embolia cutis medicamentosa, also known as Nicolau's syndrome, was described in four patients.[77–80] Three of these patients were treated with GA, and one with SC IFN-β-1a. All patients experienced acute intense pain immediately after drug injection. The clinical features consisted of dark-red skin lesions with central necrosis and lightning-like extensions. The cause of Nicolau's syndrome is most probably related to the injection rather than the injected drug.[79] Consistent with this notion, all four patients could continue their treatment without complications of DMT treatment.

Immune-mediated cutaneous adverse events

There were multiple reports of various immune-mediated and inflammatory dermatological diseases in association with DMTs. Psoriasis, a common immune-mediated inflammatory skin disease, has been reported with IFN-β treatment in three patients.[63,81,82] There were four case reports of cutaneous vasculitis as adverse cutaneous events to GA, SC IFN-β-1a, and IFN-β-1b (two patients).[83–86] Erythema elevatum diutinum, a cutaneous type of vasculitis, was described in a patient treated with SC IFN-β-1a.[87] Panniculitis was described in three patients treated with IFN-β-1b and in two patients with SC IFN-β-1a.[88–91] Nousari and colleagues described the development of cutaneous subacute lupus erythematosus in association with IM IFN-β-1a[92]. Lupus-like reactions were described in four MS patients who were treated with IFN-β-1b.[93–95] Cutaneous events with an inflammatory pathogenesis that were described only once in association with DMTs include dermatomyositis, erythema nodosum, scleromyxedema, lupus erythematosus profundus, vitiligo, and Jessner-Kanof benign lymphocytic infiltrate.[96–101]

Allergic reactions

Allergic type 1 hypersensitivity reactions were reported mainly for GA. Three patients were reported who

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developed pruritic wheals or erythema and itchy hives in response to GA injections.[102] One of these patients was suspected of an IgE-mediated reaction to GA. There was a report of exacerbation of cholinergic urticaria during GA treatment.[103] Severe systemic allergic and anaphylactic reactions were reported in association with GA as well.[104,105] Alava and colleagues described an atopic patient who developed allergic reactions to GA, and subsequently urticaria to IM IFN-β-1a.[106] Also, several reports were published on the development of widespread urticaria and angioedema to IM IFN-β-1a.[107–109] Dimov and co-workers described a severe reaction with hives and angioedema of the extremities following IM IFN-β-1a injections.[110] Brown and colleagues described an urticarial reaction in a patient treated with IFN-β-1b.[111]

Cutaneous malignancies

One case report described the association between GA and a cutaneous lymphoma in a 33-year-old female MS patient who had developed a CD30-positive, primary, cutaneous, anaplastic large-cell lymphoma after four months of GA treatment.[112] After surgical excision and radiotherapy, remission was achieved and GA could be successfully continued in this patient. Skin cancers were reported several times in association with DMTs. In a RCT comparing the efficacy and safety of fingolimod to that of IM IFN-β-1a, there were reports of a squamous cell carcinoma and a basal cell carcinoma in two patients treated with IM IFN-β-1b compared to five basal cell carcinomas and three melanomas among those treated with fingolimod.[113] Fruland and colleagues described a squamous cell carcinoma in a 47-year-old male MS patient who was treated with IFN-β-1b.[114]

Other cutaneous adverse events

Several skin reactions associated with DMTs were described only once or twice. Tai and Tam reported a fixed drug eruption associated with IFN-β-1b treatment, presenting as multiple erythematous plaques at non-injection sites.[115] Another case report described a widespread macolopapular rash following IM IFN-β-1a injections with a positive prick test to IFN-β-1a.[116] Other less frequently occurring cutaneous adverse events reported among MS patients receiving DMTs were granulomatous dermatitis, subcutaneous infiltrate, calcified subcutaneous nodule and alopecia.[117–120]

Discussion

We performed a systematic review of the literature to describe the incidence and the clinical spectrum of cutaneous adverse events in patients treated with DMTs for MS. Incidences of cutaneous adverse events were reported in several RCTs and a few prospective follow-up studies. Available data from these studies showed that a substantial proportion of MS patients receiving DMTs developed local injection-site reactions during their treatment. Up to approximately 90% of patients treated with GA and SC IFN-β had developed local skin reactions. The incidence among patients treated with IM IFN-β-1a appeared to be lower, with up to 33% of these patients developing skin reactions. There were no major differences in the occurrence of injection-site reactions between the different dosages of the DMTs. Next to the local injection-site skin reactions, there were many case reports and case series of more severe, generalized and sometimes persisting cutaneous adverse events described in association with DMTs. Frequently reported cutaneous adverse events to DMTs in MS patients were lipoatrophy, skin necrosis and ulcers. In addition, a wide variety of dermatological diseases associated with DMTs were described, including various immune-mediated inflammatory skin diseases, such as psoriasis, vasculitis, and lupus-like reactions. Most of these dermatological reactions were rare and described only once. In several cases, cessation of DMT or switching to another DMT was required.

Several limitations need to be considered. Firstly, a systematic review of adverse events is challenging with regard to the literature search. We cannot exclude the possibility that relevant articles were missed in our literature search. Secondly, definitions of skin reactions were not uniform among the included RCTs, making it difficult to compare these or to calculate a risk estimate for the incidence of skin reactions. Thirdly, RCTs in general measure only common, short-term adverse events. There were only a few observational (cross-sectional and cohort) studies available that assessed cutaneous adverse events in MS patients treated with DMTs. Case reports do provide information on the occurrence of less frequent side-effects, but a definitive causal relationship with the DMT is not always clear. Furthermore, there were only few studies that assessed cutaneous adverse events as a primary outcome.

Several mechanisms have been postulated by which DMTs induce skin reactions. Most theories focus on immune-mediated mechanisms, including local inflammatory reactions, IgE-mediated reactions, delayed hypersensitivity reactions and other immune reactions.[121] Buttmann and colleagues showed that SC IFN-β is able to induce local chemokine production, which can lead to inflammatory skin reactions.[122] Consistent with this, several of the reported cutaneous adverse events have an immune-mediated pathogenesis, such as psoriasis and vasculitis. Mechanical injury due to injections seems less likely to play an important role in the development of these cutaneous adverse events. Embolia cutis medicamentosa, however, seems to be the only exception as it is associated with the injection itself rather than with the drug injected.[79,121]

Based upon the results of our literature review lipoatrophy seemed more frequently reported in association with GA in comparison to the other DMTs. A majority of the

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cases with lipoatrophy were linked to GA. However, there were reports of lipoatrophy in two patients treated with SC IFN-β-1a and IFN-β-1b, respectively. By contrast, cutaneous necrosis was reported solely in relationship to SC IFN-β-1b. For the other types of cutaneous adverse events, there was no clear relationship with a specific DMT. Still, the evidence for the occurrence of specific adverse events associated with a specific DMT is limited given that prospective studies designed to assess the incidences of cutaneous adverse events with each DMT are lacking.

Several immune-mediated cutaneous adverse events were described in association with DMT, including associations with psoriasis, lupus erythematosus and dermatomyositis. A definite causal role of the DMT was not clearly established in most of these case-reports, making it unclear whether the associations with immune-mediated cutaneous adverse events are truly attributable to the DMT. Somani and colleagues have provided experimental evidence supporting a causal role of interferon treatment in the development of dermatomyositis as a cutaneous adverse event to DMT.[96] Still, the reported immune-mediated cutaneous events may be related to MS itself rather than to the DMT, considering the described associations between MS and other immune-mediated diseases such as inflammatory bowel disease and bullous pemphigoid.[123,124] Alternatively, treatment with DMT may pose an additional increased risk to develop immune-mediated cutaneous adverse events in patients with multiple sclerosis.

Cutaneous malignancies associated with DMT were reported in a few RCTs and case reports, but DMT-use does not seem to be associated with an increased risk of skin cancer. A French cohort study did not find an increased risk of skin cancer among MS patients treated with DMT.[125] Similarly, a recent analysis of data from several RCTs and data from a global drug safety database showed that long-term treatment with SC IFN-β-1a was not associated with malignancies, including melanoma skin cancer. However, non-melanoma skin cancers were not included in these analyses.[126]

It is interesting to compare the incidence of cutaneous adverse events associated with DMTs to that of injectable therapies for other chronic diseases, even though direct comparisons are lacking. Studies in patients with inflammatory bowel disease who were treated with subcutaneous anti-tumour necrosis factor alpha inhibitors demonstrated a relatively high incidence of skin reactions and a broad spectrum of cutaneous adverse events.[127] Similar high incidences were reported for rheumatoid arthritis patients treated with daily subcutaneous injections of a interleukin-1 receptor antagonist.[128]

The occurrence of skin reactions may lead to cessation of the DMT or switching to another type DMT. Given that dermatologists have experience in the diagnosis and treatment of immune-mediated inflammatory skin diseases, they may help in assessing and treating the skin reactions induced by DMTs without the necessity of stopping or switching the DMT.

Future research should aim at assessing the determinants of cutaneous adverse events in long-term treatment with DMT in large observational studies, such as cumulative injections, anatomical site correlations and dose dependency. Furthermore, it would be of interest to assess if there is a correlation between the occurrence of skin reactions and the efficacy of the DMT. Another interesting research question for future studies is whether cutaneous reactions to DMT are associated with a decrease in treatment adherence. In a large multicentre observational study among 2648 patients, injection-related problems were a commonly cited reason for non-adherence.[55] Furthermore, it would be relevant to assess the impact of skin reactions on patient quality of life. If there is a significant clinical impact, it would be helpful to assess interventions to prevent or reduce the onset of cutaneous adverse events. Attempts have been made already to prevent local skin reactions via oral antihistamines and warm compresses.[129,130]

In conclusion, this systematic review shows that DMTs in MS are frequently associated with local injection-site reactions and a wide range of other cutaneous adverse events.

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