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Adverse side effects of Glatiramer acetate and Interferon beta-1a in patients with multiple sclerosis: A systematic review of case reports

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Keywords
Systematic Review; Glatiramer Acetate; Interferon Beta-1a; Multiple Sclerosis; Adverse Effects

Abstract

Background: Glatiramer acetate (GA) and Interferon (IFN) beta-1a are used as first-line disease-modifying treatments for multiple sclerosis (MS). In this systematic review, we summarized case reports and case series of adverse side effects of GA and IFN beta-1a in MS patients.

Methods: Without any restrictions, PubMed, Scopus, Web of Sciences, and Embase databases, and gray literature were systemically searched until June 2022. Articles were screened and data were extracted based on a predefined table by two independent reviewers. The risk of bias was assessed using the Joanna Briggs Institute (JBI) tool.

Results: We identified 2103 records from the preliminary search. After deduplication and screening, 172 articles were included in the systematic review. In total, 229 individuals (52 men, 173 women, and 4 unknown) were included in the study. The most common adverse events were cutaneous (32.75%), hepatic (13.54%), allergic (8.3%), and neurological (5.68%) side effects. Furthermore, most reported side effects were related to autoimmune diseases or hypersensitivity reactions.

Conclusion: GA and IFN beta-1a are associated with several side effects which may be related to the immunomodulatory function of medication or other injection-related reactions.

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) with unknown etiology.

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MS has a high prevalence in young people,

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especially women of 20-40 years of age, and is a major cause of disability in this age group.[1] In 2020, approximately 2.8 million people worldwide were suffering from MS, and this number is expected to increase in the future.[2]

As there is no cure for MS, several medications are used as disease-modifying treatments to control the condition and decrease the symptoms of the disease. Glatiramer acetate (GA) and interferon (IFN) beta-1a are injectable first-line medications administrated subcutaneously (GA and IFN beta-1a) or intramuscularly (IFN beta-1a). The mechanism of action of these drugs is based on immunomodulation.[3,4] GA inhibits T cells' response to myelin antigens by binding major histocompatibility complex (MHC) of genes and IFN beta-1a works by upregulating anti-inflammatory and downregulating pro-inflammatory cytokines.[5,6] Although the effectiveness and safety of both medications have been approved in several studies,[7,8] multiple reports have shown various side effects of GA and IFN beta-1a.[9,10] Therefore, examining the side effects of GA and IFN beta-1a and recognizing their mechanisms is of great importance in the reduction of the adverse events of therapy.

Several studies have investigated the side effects of GA and IFN beta-1a in MS patients; however, no comprehensive study has reviewed the case reports of side effects.[11,12] Therefore, we aimed to conduct a systematic review of case reports and case series which have reported the side effects of GA and IFN beta-1a in patients with MS.

Materials and Methods

Data sources and searches: A comprehensive search was conducted until the 27th June 2022 in PubMed, Scopus, Web of Science, and Embase. Moreover, the gray literature, including the references of the references and the conference abstracts, were searched to find relevant articles.

The related keywords included in the search strategy were as follows: Glatiramer Acetate, Copaxone, TV 5010, Interferon beta-1a, Rebif, Avonex, Case Reports, Case Study, Case History, and Case Series.

Eligibility criteria: The inclusion criteria were all case reports and case series reporting side effects of GA or IFN beta-1a in MS patients.

Articles were excluded if they had any of the following criteria: 1) review articles which did not report a new case, 2) articles which were not published in English, and 3) articles reporting cases of administration of drugs other than GA and IFN beta-1a.

Study selection and data collection: One researcher removed the duplicate articles. Subsequently, two independent authors chose relevant articles by screening the title/abstract of articles based on the inclusion/exclusion criteria. Then, two authors independently reviewed the full text of the obtained articles to extract data.

Two independent researchers extracted the authors' names, publication date, country, study population, gender, mean age, type of medication, medication dosage, duration of treatment, and reported side effects based on a predefined data extraction table. The characteristics of the included articles and their demographic data are presented in table 1.

Evaluating the risk of bias: Quality assessment was performed independently by two authors using the Joanna Briggs institute (JBI) checklist for case report and case series in order to rate the quality of the included studies.[13,14]

Results

We identified 2103 records from the preliminary search. After removing duplicates, 1593 articles remained for title/abstract screening. Subsequently, 1305 records were excluded in the title/abstract screening and 114 articles were excluded after reviewing full articles. Consequently, 174 articles were included in the systematic review (Figure 1), 5 of which were case series and the remaining were case reports.Ohtani et al., 2017: Drug holiday therapy of fingolimod in Japanese relapsing-remitting multiple sclerosis.[9]

Table 1 summarizes the characteristics of patients included in the study. In total, 229 individuals (52 men, 173 women, and 4 unknown) had reported side effects related to the IFN beta-1a or GA. The age of patients was within the range of 11-73 years. Among the cases included in the study, 64.19% had been treated with IFN beta-1a. Furthermore, the duration of treatment before the onset of side effects varied from first use of medication to 14 years of treatment. The most common adverse events reported were cutaneous (32.75%), hepatic (13.54%), allergic (8.3%), and neurological (5.68%) side effects. Furthermore, most reported side effects were related to autoimmune diseases or hypersensitivity, including systemic and local reactions. Tables 2 and 3 present the result of quality assessment of the included study.

Table 1. Study characteristics

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Cutaneous side effects									
Vlahova et al.[19]	Germany	CR	1	M	55	GA	NS	40 mg 3 times per week	5 years
Koontz and Alshekhlee[20]	US	CR	1	M	55	IFN beta-1a	NS	-	First use of medication
Harde and Schwarz[21]	Germany	CR	1	M	59	GA	NS	20 mg per day	6 years
Kimbrough and Newsome[22]	US	CR	2	F	38.5	GA	NS	20 mg	2 years/3 years
Esme et al.[23]	Turkey	CR	1	F	34	GA	NS	3 times weekly	18 months
Minciullo et al.[24]	Italy	CR	1	F	45	GA	Flare up reaction	20 mg	First use of medication
Sanchez-Gonzalez et al.[25]	Spain	CR	1	F	37	GA	Flare up reaction at injection site	20 mg per day	First use of medication
Watkins et al.[26]	US	CR	1	F	36	GA	Lobular panniculitis and skin necrosis	20 mg per day	1 year
Macbeth et al.[27]	UK	CR	1	F	24	IFN beta-1a	Calcified subcutaneous nodules	44 mcg 3 times a week	3 years
Haltmeier et al.[28]	Switzerland	CR	1	F	39	GA	Contact dermatitis	-	2 months
Longmuir et al.[29]	US	CR	1	M	40	IFN beta-1a	Cotton wool spots	44 mcg 3 times per week	9 months
Kolb-Maurer et al.[30]	Germany	CR	1	F	25	IFN beta-1a	Erythematous plaque on abdomen and lower extremities	44 mcg per week	12 months
Howard and Bomprezzi[31]	US	CR	1	M	33	IFN beta-1a	Worsening of psoriasis	-	-
Frohman et al.[32]	US	CR	2	M	44	IFN beta-1a / GA	Diffuse subcutaneous edema, myositis, and myonecrosis/localized skin erythema	-	3 years/5 years
Edgar et al.[33]	Canada	CR	5	F	49.6	GA	Lipoatrophy	-	45 months/3 years/30 months/2 years/20 months
Hwang and Orengo[34]	US	CR	1	F	35	GA	Lipoatrophy	-	2 years
Beiske and Myhr[35]	Norway	CR	1	F	38	IFN beta-1a	Lipoatrophy	22 mcg three times a week	6 years
Weise et al.[36]	Germany	CR	1	F	42	IFN beta-1a	Lobular panniculitis and lipoatrophy	-	2 years
Ball et al.[37]	Canada	CR	2	F	44.5	GA	Lobular panniculitis at injection site	-	5 years/3 years
Ball et al.[38]	Canada	CS	5	4 F/1 M	51.8	IFN beta-1a	Lobular panniculitis at injection site	-	22 months/4 months/53 months/63 months/67 months
Garcia et al.[39]	Spain	CR	1	M	44	IFN beta-1a	Nodular erythematous of injection site	-	First use of medication

Table 1. Study characteristics (continue)

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Soos et al.[40]	Germany	CR	1	F	46	GA	Localized panniculitis and lipoatrophy	20 mg per day	18 months
Bosca et al.[41]	Spain	CR	2	1 F/1 M	32.5	GA	Necrotizing cutaneous lesions	-	16 months/18 months
McDaniel and Trankiem[42]	US	CR	1	M	57	IFN beta-1a	Necrotizing fasciitis	-	14 years
Carotenuto et al.[43]	Italy	CR	1	M	52	GA	Necrotizing skin lesion and radial nerve palsy	20 mg per day	21 months
Feldmann et al.[44]	Austria	CR	1	F	55	GA	Necrotizing skin lesion with muscle tissue	20 mg per day	2 years
Lopez-Lerma et al.[45]	Spain	CR	1	M	37	IFN beta-1a	Psoriasis	44 mcg 3 times a week	3 months
Mott et al.[46]	US	CR	1	F	51	GA	NS and localized panniculitis	20 mg per day	7 years
Koller and Kranke[47]	Austria	CR	1	F	39	GA	NS	-	2 years
Cicek et al.[48]	Turkey	CR	1	F	48	GA	Urticarial vasculitis	-	3 months
Kocer et al.[49]	Turkey	CR	1	F	33	IFN beta-1a	Vitiligo	22 mcg 3 times a week	2 years
Serarslan et al.[50]	Turkey	CR	1	F	41	IFN beta-1a	Widespread maculopapular rash	30 mcg per week	2 weeks
Guijarro et al.[51]	Spain	CR	2	1 F/1 M	37	IFN beta-1a	Widespread urticaria	22 mcg once a week	7 week/5 months
Fabi et al.[52]	US	CR	1	F	40	GA	Localized lipoatrophy	-	7 years
Mazzeo et al.[53]	Italy	CR	1	F	30	IFN beta-1a	Urticaria	22 mcg once a week	13 months (side effect was seen in the first use after interruption for 8 months)
Peterson et al.[54]	US	CR	1	F	55	IFN beta-1a	Morphea	-	6 years
Aviv et al.[55]	Israel	CR	12	F	40.92	GA	Lipoatrophy, erythematous urticarial plaques and nodules at injection site	-	121 months/8 months/34 months/5 months/15 months/71 months/2 months/52 months/3 months/ 6 months/8 months/120 months
Tsivgoulis et al.[56]	Greece	CR	1	F	26	IFN beta-1a	Psoriasis flare	-	4 months
Zecca et al.[57]	Switzerland	CR	1	F	58	GA	Recurrent NS	-	9 years
Bonaci-Nikolic et al.[58]	Serbia	CR	1	F	43	IFN beta-1a	SLE	33 mcg 3 times a week	32 months
Crispin and Diaz-Jouanen[59]	Mexico	CR	1	F	47	IFN beta-1a	SLE	44 mcg twice a week	3 years

Table 1. Study characteristics (continue)

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Bahri et al.[60]	Tunisia	CR	1	F	34	IFN beta-1a	SLE	-	9 months
Bezalel et al.[61]	Canada	CR	1	F	52	IFN beta-1a	Morphea	-	6 months
Somani et al.[62]	US	CR	1	M	57	IFN beta-1a	Dermatomyositis	30 mcg once a week	5 years
Pacheco et al.[63]	US	CR	1	F	42	GA	Reversible alopecia	-	2 years
Ozuguz et al.[64]	Turkey	CR	1	F	44	IFN beta-1a	Septal panniculitis	-	10 days
Nousari et al.[65]	US	CR	1	M	43	IFN beta-1a	SCLE	11 mcg per week	5 months
Vera-Iglesias et al.[66]	Spain	CR	1	F	22	IFN beta-1a	Halo nevus	22 mcg 3 times a week	3 months
Thouvenot et al.[67]	France	CR	1	F	55	GA	Erythema nodosum	20 mg per day	3 months
Ozden et al.[68]	Turkey	CR	1	F	38	IFN beta-1a	Dermal fibrosis and cutaneous necrosis	44 mcg twice a week	5 years
Gil et al.[69]	Switzerland	CR	1	F	42	IFN beta-1a	EED	-	1 year
Hepatic side effects									
Christopher et al.[70]	UK	CR	1	F	38	IFN beta-1a	Acute hepatitis	22 mcg 3 time a week	21 months
Kozielewicz and Pawlowska[71]	Poland	CR	1	F	42	IFN beta-1a	Fulminant liver failure	30 mcg once a week	4 weeks
Duchini[72]	US	CR	1	F	38	IFN beta-1a	AIH	-	24 months
Yamaguchi et al.[73]	Japan	CR	1	M	44	IFN beta-1a	AIH	7.5 mcg	5 days
Mishra et al.[74]	Canada	CR	1	F	43	IFN beta-1a	AIH	44 mg 3 times a week	3 months
Yamazaki et al.[75]	Japan	CR	1	F	44	IFN beta-1a	Fulminant hepatitis	30 mcg once a week	10 weeks
Sabatino et al.[76]	US	CR	1	F	36	GA	Acute liver injury	-	13 days
Liao et al.[77]	Taiwan	CR	2	F	49.5	IFN beta-1a	Delayed liver function impairment	44 mcg 3 times per week	79 months/5 years
Sinagra et al.[78]	Italy	CR	2	F	35	GA	AIH	-	1 month
Byrnes et al.[79]	US	CR	3	F	34.67	IFN beta-1a	Liver injury	30 mcg once a week/ 70.4 mcg single dose/ 22 mcg once a week	10 months/one cumulative dose/ 2 weeks
Michels et al.[80]	Germany	CR	1	F	23	GA	Liver injury	-	-
Onmez et al.[81]	Turkey	CR	1	F	36	GA	Liver injury	20 mg per day	1 month
Pietrosi et al.[82]	Italy	CR	1	F	46	IFN beta-1a	Fulminant hepatic failure	30 mcg once a week	1.5 months
Yoshida et al.[83]	Canada	CR	1	F	59	IFN beta-1a	Fulminant hepatic failure	22 mcg three times a week	7 weeks
Neumann et al.[84]	Germany	CR	1	M	71	GA	AIH	20 mg per day	4 months
Subramaniam et al.[85]	Australia	CR	1	F	31	GA	Hepatotoxicity	20 mg per day	2 months
Antezana et al.[86]	US	CR	1	F	28	GA	Hepatotoxicity	-	6 months
Makhani et al.[87]	Canada	CR	1	F	15	GA	Hepatotoxicity	20 mg per day	2 months
Flaire et al.[88]	France	CR	1	F	56	GA	Hepatitis	-	3 months
La Gioia et al.[89]	Italy	CR	1	F	25	GA	Hepatitis	-	8 months
Villamil et al.[90]	Argentina	CR	2	1 F/1 M	38.5	IFN beta-1a	AIH	-	18 months/ 41 months
Almeida et al.[91]	Spain	CR	1	F	65	GA	Liver injury	-	-
Francis et al.[92]	US	CR	1	F	52	IFN beta-1a	Liver injury	8.8 mg per day	1 week

Table 1. Study characteristics (continue)

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Grieco et al.[93]	Italy	CR	1	F	43	IFN beta-1a	Severe acute hepatitis	44 mcg a week	3 years
Kowalec et al.[94]	Canada	CR	1	F	42	IFN beta-1a	AIH and PBC	44 mcg 3 times a week	5 months
Pulicken et al.[95]	US	CR	1	F	43	IFN beta-1a	AIH	44 mcg 3 times a week	6 weeks
Allergic reaction									
Baumgartner et al.[96]	Germany	CR	6	5 F/1 M	27.17	GA	Anaphylactic reaction	-	3 months/6 months/6 months/3 months/3 months/ 3 months
Wohrl et al.[97]	Austria	CR	2	F	31.5	GA	Anaphylactic reaction	20 mg a day	3 months/ -
Crestani et al.[98]	US	CR	1	F	14	GA	Hypersensitivity	20 mg per day	18 months
Marco-Martin et al.[99]	Spain	CR	6	2 F/4 M	34.5	GA	Hypersensitivity	20 mg per day	5 cases: First use of medication/one case: 1 year
Mayorga et al.[100]	Spain	CR	2	F	44	IFN beta-1a	Hypersensitivity	-	5 months/first use of medication
Rauschka et al.[101]	Germany	CR	1	F	31	GA	Severe anaphylactic reaction	-	10 month
Cortellini et al.[102]	Italy	CR	1	F	34	IFN beta-1a	Anaphylactic reaction	One time in 2 days	3 months
Neurological side effects									
Motta et al.[103]	Poland	CR	1	M	43	GA	GBS	-	1 year
Frese et al.[104]	Germany	CR	1	F	35	GA	MG	-	18 months
Pawlitzki et al.[105]	Germany	CR	1	-	35	IFN beta-1a	Presence of anti-myelin oligodendrocyte glycoprotein autoantibody	-	5 months
Coraci et al.[106]	Italy	CR	1	F	30	GA	Ulnar neuropathy	-	First use of medication
Villa et al.[107]	Argentina	CR	3	-	-	IFN beta-1a	Presence of antibody in CSF	-	6-24 months
Bischof and Sprenger[108]	Switzerland	CR	1	F	49	IFN beta-1a	Recurrence of trigeminal neuropathy	30 mcg	3 weeks
Lagueny and Ouallet[109]	France	CR	1	F	45	GA	Meralgia paresthetica	-	7 years
Ekstein et al.[110]	Israel	CR	1	F	34	IFN beta-1a	Polyneuropathy	-	6 years
Polman et al.[111]	The Netherlands	CR	1	F	54	IFN beta-1a	Relapsing encephalopathy	22 mcg 3 times a week	20 years
Strohm et al.[112]	US	CR	1	F	20	IFN beta-1a	Reversible cerebral vasoconstriction syndrome	-	2 months
Von et al.[113]	France	CR	1	M	21	IFN beta-1a	Acute demyelinating disease	33 mcg once a week	3 weeks
Renal side effects									
Hansen et al.[114]	UK	CR	1	M	41	IFN beta-1a	AKI, SLE, and TMA	22 mcg 3 times a week	1 year
Tornes et al.[115]	US	CR	1	F	41	IFN beta-1a	FSGS	44 mcg 3 times per week	4 months
Capobianco et al.[116]	Italy	CR	1	F	22	IFN beta-1a	Glomerulonephritis and sarcoid-like lung disease	44 mcg 3 times a week	13 years
Ozturk et al.[117]	Turkey	CR	1	M	32	IFN beta-1a	FSGS	44 mcg 3 times a week	6 years

Table 1. Study characteristics (continue)

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Tola et al.[118]	Italy	CR	1	M	39	IFN beta-1a	Recurrent nephrotic syndrome	-	2 months
Evans et al.[119]	UK	CR	1	F	43	IFN beta-1a	FSGS	22 mcg per week	15 months
Auty and Saleh[120]	UAE	CR	1	M	28	IFN beta-1a	Nephrotic syndrome	30 mcg once a week	2 years
Yuste et al.[121]	UK	CR	1	F	37	IFN beta-1a	Glomerulonephritis	44 mcg 3 times a week	9 years
Gucev et al.[122]	Macedonia	CR	1	F	11	IFN beta-1a	PRS (medication used by mother during pregnancy)	-	-
Mahe et al.[123]	France	CR	1	F	38	IFN beta-1a	Renal TMA	-	5 years
Li et al.[124]	Italy	CR	1	F	36	IFN beta-1a	Renal TMA	22 mcg 3 times a week	3 months
Neoplasm									
Almeida et al.[125]	Brazil	CR	2	1 F/1 M	30.5	IFN beta-1a	CML	30 mcg once a week / 22 mcg 3 times a week	8 months/6 months
Vieira et al.[126]	Brazil	CR	1	F	39	GA	Meningioma	-	3 years
Gama et al.[127]	Brazil	CR	1	F	51	IFN beta-1a	Meningioma	22 mcg 3 times a week, 30 mcg once a week	5 years, 3 years
Walker et al.[128]	Canada	CR	1	F	43	GA	Malignant melanoma	20 mg a week	-
Chiang et al.[129]	US	CR	1	F	61	IFN beta-1a	CNS lymphoma	-	10 years
Blancas et al.[130]	Spain	CR	1	M	33	IFN beta-1a	Relapse of non-seminomatous testicular cancer	44 mcg 3 times a week	2 years
Amaria et al.[131]	US	CR	2	F	50.5	IFN beta-1a/GA	Breast cancer	-	1 year/20 months
Microangiopathy									
Gerischer et al.[132]	Germany	CR	1	F	53	IFN beta-1a	TMA	44 mcg 3 times per week	14 years
Yam et al.[133]	Australia	CR	1	F	57	IFN beta-1a	TMA	44 mcg 3 times a week	20 years
Perez et al.[134]	Spain	CR	1	F	48	IFN beta-1a	TMA and hypertension	-	9 years
Olea et al.[135]	Spain	CR	1	F	37	IFN beta-1a	TMA	-	5 months
Allinovi et al.[136]	Italy	CR	3	2 F/1 M	37.33	IFN beta-1a	TMA	-	15 years/ 11 years/12 years
Thyroid side effect									
Heesen et al.[137]	Germany	CR	1	F	30	GA	Autoimmune hyperthyroidism	-	3 years
Strueby et al.[138]	Canada	CR	2	F	37.5	IFN beta-1a	Arthritis/autoimmune thyroid disease and bursitis	22 mcg 3 times a week	2 weeks/50 months
Kreiss et al.[139]	Israel	CR	1	F	28	IFN beta-1a	Subacute thyroiditis	22 mcg once a week	2 months
Ocular side effects									
Spierer and Leibovitch[140]	Israel	CR	1	F	59	IFN beta-1a	Recurrent orbital inflammation	22 mcg 3 times a week	10 years
Gaetani et al.[141]	Italy	CR	1	F	37	IFN beta-1a	Retinopathy	44 mcg 3 times a week	12 months
Bakri and Swanson[142]	US	CR	1	F	49	IFN beta-1a	Asymptomatic peripheral retinal hemorrhages	44 mcg 3 times a week	4 years
Post and Colleaux[143]	Canada	CR	1	F	42	IFN beta-1a	Retinopathy	44 mcg 3 times a week	5 months
Psychological side effects									

Table 1. Study characteristics (continue)

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Goeb et al.[144]	France	CR	1	M	37	IFN beta-1a	Delirium, delusion, and depression	22 microgram (mcg) 3 times a week	8 months
Pandya and Patten[145]	Canada	CR	1	F	42	IFN beta-1a	Depression	-	6 months
Lana-Peixoto et al.[146]	Brazil	CR	1	M	21	IFN beta-1a	Depression and suicidal ideation	22 mcg 3 times a week	5 years
Lamotte et al.[147]	France	CR	1	F	21	IFN beta-1a	Psychosis	-	15 months
Pjrek et al.[148]	Austria	CR	1	F	27	GA	Psychosis	20 mg per day	7 years
Cardiac side effect									
Kastalli et al.[149]	Tunisia	CR	1	F	35	IFN beta-1a	Cardiac arrhythmia	30 mcg per week	56 months
Michaud et al.[150]	US	CR	1	F	59	GA	EM	20 mg per day	16 years
Cheraghmakani et al.[151]	Iran	CR	1	F	43	IFN beta-1a	Cardiomyopathy	44 mcg 3 times a week	36 months
Inflammatory bowel disease									
Rodrigues et al.[152]	Portugal	CS	4	1 F/3 M	23.75	IFN beta-1a	Ulcerative colitis	22 mcg once a week/ 22 mcg 3 times a week/22 mcg/22 mcg	3 years/1 year/4.5 years/4 months
Charach et al.[153]	Israel	CR	1	F	27	GA	Crohn's disease	20 mg per day	2 years
Schott et al.[154]	Germany	CR	1	F	29	IFN beta-1a	Ulcerative colitis	30 mcg	12 months
Tuna et al.[155]	Turkey	CR	1	F	44	IFN beta-1a	Ulcerative colitis	33 mcg once a week	1 week
Pulmonary side effects									
Ferriby and Stojkovic[156]	France	CR	1	M	49	IFN beta-1a	BO and organizing pneumonia	30 mcg per week	3 months
Fok et al.[157]	Australia	CR	2	F	50	IFN beta-1a	PAH	-	9 years/6 years
Govern et al.[158]	Ireland	CR	1	F	45	IFN beta-1a	PAH	-	5 years
Piroddi et al.[159]	Italy	CR	1	F	47	IFN beta-1a	Severe respiratory failure due to pulmonary hypertension	44 mcg 3 times a week	3 years
Caravita et al.[160]	Italy	CR	1	F	59	IFN beta-1a	Pulmonary hypertension	-	1 year
Viral disease									
Halasan et al.[161]	US	CR	1	M	73	GA	Disseminated herpes zoster	-	8 years
Lehmann et al.[162]	Germany	CR	1	F	46	IFN beta-1a	PML	30 mcg once a week	8 months
Muscular side effects									
Jerman et al.[163]	Slovenia	CR	1	F	35	IFN beta-1a	Rhabdomyolysis	30 mcg once a week	10 months
Lunemann et al.[164]	Germany	CR	1	M	39	IFN beta-1a	Rhabdomyolysis	22 mcg 3 times a week	4 months
Dalbjerg et al.[165]	Denmark	CR	1	M	30	IFN beta-1a	Rhabdomyolysis	44 mcg 3 times a week	7 months
Other side effects									
Aslam and Singh[166]	US	CR	1	F	42	IFN beta-1a	Aplastic anemia	-	1 year
Masuda et al.[167]	Japan	CR	1	F	53	IFN beta-1a	Bilateral foot acrocyanosis	-	2 months
Uonaga et al.[168]	Japan	CR	1	F	57	IFN beta-1a	Type 1 DM	22 mcg once a week	13 months
Ferguson[169]	US	CR	1	F	40	GA	Serum sickness	40 mg 3 times a week	5 months

Table 1. Study characteristics (continue)

Study	Country	Type of study	Number of patients	Gender	Mean age (year)	Medication	Side effect	Dose	Duration of treatment
Viana de Andrade et al.[170]	Brazil	CR	1	F	43	IFN beta-1a	Systemic sarcoidosis and xanthoma planum	-	3 years
Powell et al.[171]	Australia	CR	1	F	38	IFN beta-1a	Systemic sclerosis	-	4 months
Salahudheen and Begam[172]	UAE	CR	1	F	30	IFN beta-1a	Placental insufficiency	30 mcg once a week	5 years
Laird et al.[173]	US	CR	1	M	23	IFN beta-1a	Exacerbation of Susac syndrome	-	15 months
Eguchi et al.[174]	Japan	CR	1	F	34	IFN beta-1a	HDL binding protein 1 autoantibody syndrome	-	-
Nerrant et al.[175]	France	CR	1	F	38	IFN beta-1a	HUS	22 mcg 3 times a week	7 months
Levesque et al.[176]	US	CR	1	F	69	IFN beta-1a	Polyarthritis	30 mcg once a week	16 weeks
Andreassen et al.[177]	US	CR	1	F	34	IFN beta-1a	Acromegaly	44 mcg 3 times a week	8 years
Nolden et al.[178]	Germany	CR	1	M	40	GA	Jessner lymphocytic infiltrate	20 mg per day	First use of medication
Midgard et al.[179]	Norway	CR	1	M	53	IFN beta-1a	Acute pancreatitis	22 mcg 3 times a week	8 weeks
de Santi et al.[180]	Italy	CR	1	F	48	IFN beta-1a	pSS	30 mcg once a week	5 years
Kawahara et al.[181]	Japan	CR	1	F	34	IFN beta-1a	Hypertriglyceridemia	30 mcg	1 year
de Massougnes et al.[182]	Switzerland	CR	2	M	46.5	IFN beta-1a	Peripheral bilateral telangiectasia	44 mcg 3 times a week	3 years/9 years
Kinyas and Esgin[183]	Turkey	CR	1	F	40	IFN beta-1a	Peripheral vasculitis and IU	30 mcg once a week	7 years
Chakravarty et al.[184]	US	CR	1	M	39	IFN beta-1a	Sarcoidosis	-	3 years
Kumar and Rodriguez[185]	US	CR	1	F	37	IFN beta-1a	Scleromyxedema and monoclonal gammopathy	-	3 years
Cosso et al.[186]	Italy	CR	1	F	57	IFN beta-1a	HLH	-	5 months
Diamantopoulos et al.[187]	Norway	CR	1	F	52	IFN beta-1a	Deterioration of Takayasu arteritis	-	10 years
Chang et al.[188]	Taiwan	CR	1	F	19	IFN beta-1a	Severe necrosis and cellulitis	44 mcg 3 times a week	3 years
Larochelle et al.[189]	Canada	CR	3	F	40.67	IFN beta-1a	TTP-HUS	44 mcg 3 times a week	14 months/132 months/60 months
Tavakoli et al.[190]	Iran	CR	1	M	30	IFN beta-1a	Ecchymosis on arms, epistaxis, abnormal CBC and high urea, and Cr level of plasma	44 mcg 3 times a week	3 months
Roskal-Walek et al.[191]	Poland	CR	1	F	20	IFN beta-1a and GA	Susac syndrome	-	7 weeks/2 weeks
Niessen et al.[192]	Germany	CR	1	F	49	GA	Aseptic meningitis	40 mg 3 times weekly	5 days

CR: Case report; CS: Case series; M: Male; F: Female; PRS: Papillorenal syndrome; FSGS: Focal segmental glomerulosclerosis; NS: Nicolau syndrome; SLE: Systemic lupus erythematosus; SCLE: Subacute cutaneous lupus erythematosus; EED: Erythema elevatum diutinum; AIH: Autoimmune Hepatitis; PBC: Primary biliary cirrhosis; GBS: Guillain-Barre syndrome; MG: Myasthenia gravis; CSF: Cerebrospinal fluid; TMA: Thrombotic microangiopathy; CML: Chronic myeloid leukemia; EM: Eosinophilic myocarditis; BO: Bronchiolitis obliterans; PAH: Pulmonary arterial hypertension; PML: Progressive multifocal leukoencephalopathy; DM: Diabetes mellitus; HDL: High density lipoprotein; HUS: Hemolytic uremic syndrome; pSS: Primary Sjögren's syndrome; IU: Intermediate uveitis; HLH: Hemophagocytic lymphohistiocytosis; TTP: Thrombotic thrombocytopenic purpura; CBC: Complete blood count ; Cr: Creatinine; AKI: Acute Kidney Injury

Table 2. Quality assessment of case reports

Study	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
Goeb et al.[144]	*	*	*	*	*	*	*	*	8
Von et al.[113]	*	*	*	*	*	*	*	*	8
Christopher et al.[70]	*	*	*	*	*	*	*	*	8
Kozielewicz and Pawlowska[71]	*	*	*	*	*	*	*	*	8
Hansen et al.[114]	*	*	*	*	*	*	*	*	8
Wohrl et al.[97]	*	*	*	*	*	*	*	*	8
Bonaci-Nikolic et al.[58]	*	*	*	*	*	*	*	*	8
Aslam and Singh[166]		*	*	*	*	*	*	*	7
Strueby et al.[138]	*	*	*	*	*	*	*	*	8
Walker et al.[128]	*	*	*	*	*	*	*	*	8
Bakri and Swanson[142]	*	*	*	*	*	*	*	*	8
Duchini[72]		*	*	*	*	*	*	*	7
Yamaguchi et al.[73]	*	*	*	*	*	*	*	*	8
Mishra et al.[74]	*	*	*	*	*	*	*	*	8
Heesen et al.[137]		*	*	*	*	*	*	*	7
Yamazaki et al.[75]	*	*	*	*	*	*	*	*	8
Masuda et al.[167]		*	*	*	*	*	*	*	7
Macbeth et al.[27]	*	*	*	*	*	*	*	*	8
Kastalli et al.[149]	*	*	*	*	*	*	*	*	8
Halasan et al.[161]		*	*	*	*	*	*	*	7
Ozuguz et al.[64]		*	*	*	*	*	*	*	7
Uonaga et al.[168]	*	*	*	*	*	*	*	*	8
Ferguson[169]	*	*	*	*	*	*	*	*	8
Kimbrough and Newsome[22]	*	*	*	*	*	*	*	*	8
Almeida et al.[125]	*	*	*	*	*	*	*	*	8
Ferriby and Stojkovic[156]	*	*		*		*	*	*	6
Sabatino et al.[76]		*	*	*	*	*	*	*	7
Haltmeier et al.[28]		*	*	*	*	*	*	*	7

Table 2. Quality assessment of case reports (continue)

Study	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
Longmuir et al.[29]	*	*	*	*	*	*	*	*	8
Kolb-Maurer et al.[30]	*	*	*	*	*	*	*	*	8
Liao et al.[77]	*	*	*	*	*	*	*	*	8
Howard and Bomprezzi[31]		*	*	*	*	*	*	*	7
Pandya and Patten[145]		*	*	*	*	*	*	*	7
Ozden et al.[68]	*	*	*	*	*	*	*	*	8
Charach et al.[153]	*	*	*	*	*	*	*	*	8
Motta et al.[103]		*	*	*	*	*	*	*	7
Frese et al.[104]		*	*	*	*	*	*	*	7
Viana de Andrade et al.[170]		*	*	*	*	*	*	*	7
Powell et al.[171]		*	*	*	*	*	*	*	7
Schott et al.[154]	*	*	*	*	*	*	*	*	8
Michaud et al.[150]	*	*	*	*	*	*	*	*	8
Frohman et al.[32]		*	*	*	*	*	*	*	7
Salahudheen and Begam[172]	*	*	*	*	*	*	*	*	8
Sinagra et al.[78]		*	*	*	*	*	*	*	7
Byrnes et al.[79]	*	*	*	*	*	*	*	*	8
Michels et al.[80]		*	*	*	*	*	*	*	7
Onmez et al.[81]	*	*	*	*	*	*	*	*	8
Vlahova et al.[19]	*	*	*	*	*	*	*	*	8
Koontz and Alshekhlee [20]		*	*	*	*	*	*	*	7
Harde and Schwarz[21]	*	*	*	*	*	*	*	*	8
Gil et al.[69]		*	*	*	*	*	*	*	7
Thouvenot et al.[67]	*	*	*	*	*	*	*	*	8
Laird et al.[173]		*	*	*	*	*	*	*	7
Gerischer et al.[132]	*	*	*	*	*	*	*	*	8
Minciullo et al.[24]	*	*	*	*	*	*	*	*	8
Sanchez-Gonzalez et al.[25]	*	*	*	*	*	*	*	*	8

Table 2. Quality assessment of case reports (continue)

Study	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
Tornes et al.[115]	*	*	*	*	*	*	*	*	8
Pietrosi et al.[82]	*	*	*	*	*	*	*	*	8
Yoshida et al.[83]	*	*	*	*	*	*	*	*	8
Neumann et al.[84]	*	*	*	*	*	*	*	*	8
Subramaniam et al.[85]	*	*	*	*	*	*	*	*	8
Antezana[86]				*	*	*	*	*	5
Makhani et al.[87]	*	*	*	*	*	*	*	*	8
Flaire et al.[88]		*	*	*	*	*	*	*	7
La Gioia et al.[89]		*	*	*	*	*	*	*	7
Watkins et al.[26]	*	*	*	*	*	*	*	*	8
Eguchi et al.[174]		*	*	*	*	*	*	*	7
Vera-Iglesias et al.[66]	*	*	*	*	*	*	*	*	8
Nerrant et al.[175]	*	*	*	*	*	*	*	*	8
Crestani et al.[98]	*	*	*	*	*	*	*	*	8
Mayorga et al.[100]		*	*	*	*	*	*	*	7
Villa et al.[107]		*	*	*	*	*	*	*	7
Cheraghmakani et al.[151]	*	*	*	*	*	*	*	*	8
Fok et al.[157]		*	*	*	*	*	*	*	7
Lana-Peixoto et al.[146]	*	*	*	*	*	*	*	*	8
Bezalel et al.[61]		*	*	*	*	*	*	*	7
Villamil et al.[90]		*	*	*	*	*	*	*	7
Govern et al.[158]		*	*	*	*	*	*	*	7
Post and Colleaux[143]	*	*	*	*	*	*	*	*	8
Bischof and Sprenger[108]	*	*	*	*	*	*	*	*	8
Capobianco et al.[116]	*	*	*	*	*	*	*	*	8
Ozturk et al.[117]	*	*	*	*	*	*	*	*	8
Yam et al.[133]	*	*	*	*	*	*	*	*	8
Levesque et al.[176]	*	*	*	*	*	*	*	*	8
Lamotte et al.[147]		*	*	*	*	*	*	*	7

Table 2. Quality assessment of case reports (continue)

Study	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
Andreassen et al.[177]	*	*	*	*	*	*	*	*	8
Nolden et al.[178]	*	*	*	*	*	*	*	*	8
Blancas et al.[130]	*	*	*	*	*	*	*	*	8
Midgard et al.[179]	*	*	*	*	*	*	*	*	8
Edgar et al.[33]		*	*	*	*	*	*	*	7
Hwang and Orengo[34]		*	*	*	*	*	*	*	7
Beiske and Myhr[35]	*	*	*	*	*	*	*	*	8
Almeida et al.[91]		*	*	*	*	*	*	*	7
Francis et al.[92]	*	*	*	*	*	*	*	*	8
Weise et al.[36]		*	*	*	*	*	*	*	7
Ball et al.[37]		*	*	*	*	*	*	*	7
Garcia et al.[39]		*	*	*	*	*	*	*	7
Soos et al.[40]	*	*	*	*	*	*	*	*	8
de Santi et al.[180]	*	*	*	*	*	*	*	*	8
Kawahara et al.[181]	*	*	*	*	*	*	*	*	8
Vieira et al.[126]		*	*	*	*	*	*	*	7
Gama et al.[127]	*	*	*	*	*	*	*	*	8
Lagueny and Ouallet[109]		*	*	*	*	*	*	*	7
Peterson et al.[54]			*	*	*	*	*	*	6
Bosca et al.[41]		*	*	*	*	*	*	*	7
McDaniel and Trankiem[42]		*	*	*	*	*	*	*	7
Carotenuto et al.[43]	*	*	*	*	*	*	*	*	8
Feldmann et al.[44]	*	*	*	*	*	*	*	*	8
Auty and Saleh[120]	*	*	*	*	*	*	*	*	8
Yuste et al.[121]	*	*	*	*	*	*	*	*	8
Lopez-Lerma et al.[45]	*	*	*	*	*	*	*	*	8
Mott et al.[46]	*	*	*	*	*	*	*	*	8
Koller and Kranke[47]		*	*	*	*	*	*	*	7
Gucev et al.[122]		*	*	*	*	*	*	*	7
Chiang et al.[129]		*	*	*	*	*	*	*	7

Table 2. Quality assessment of case reports (continue)

Study	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
de Massougnes et al.[182]	*	*	*	*	*	*	*	*	8
Kinyas and Esgin[183]	*	*	*	*	*	*	*	*	8
Ekstein et al.[110]		*	*	*	*	*	*	*	7
Lehmann et al.[162]	*	*	*	*	*	*	*	*	8
Pjrek et al.[148]	*	*	*	*	*	*	*	*	8
Tuna et al.[155]	*	*	*	*	*	*	*	*	8
Polman et al.[111]	*	*	*	*	*	*	*	*	8
Tola et al.[118]		*	*	*	*	*	*	*	7
Zecca et al.[57]		*	*	*	*	*	*	*	7
Spierer and Leibovitch[140]	*	*	*	*	*	*	*	*	8
Mahe et al.[123]		*	*	*	*	*	*	*	7
Li et al.[124]	*	*	*	*	*	*	*	*	8
Gaetani et al.[141]	*	*	*	*	*	*	*	*	8
Pacheco et al.[63]		*	*	*	*	*	*	*	7
Strohm et al.[112]		*	*	*	*	*	*	*	7
Jerman et al.[163]	*	*	*	*	*	*	*	*	8
Lunemann et al.[164]	*	*	*	*	*	*	*	*	8
Dalbjerg et al.[165]	*	*	*	*	*	*	*	*	8
Chakravarty et al.[184]		*	*	*	*	*	*	*	7
Kumar and Rodriguez[185]		*	*	*	*	*	*	*	7
Cosso et al.[186]		*	*	*	*	*	*	*	7
Grieco et al.[93]	*	*	*	*	*	*	*	*	8
Rauschka et al.[101]		*	*	*	*	*	*	*	7
Somani et al.[62]	*	*	*	*	*	*	*	*	8
Diamantopoulos et al.[187]		*	*	*	*	*	*	*	7
Chang et al.[188]	*	*	*	*	*	*	*	*	8
Piroddi et al.[159]	*	*	*	*	*	*	*	*	8
Mazzeo et al.[53]	*	*	*	*	*	*	*	*	8
Caravita et al.[160]		*	*	*	*	*	*	*	7

Table 2. Quality assessment of case reports (continue)

Study	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
Nousari et al.[65]	*	*	*	*	*	*	*	*	8
Kreiss et al.[139]	*	*	*	*	*	*	*	*	8
Kowalec et al.[94]	*	*	*	*	*	*	*	*	8
Bahri et al.[60]		*	*	*	*	*	*	*	7
Crispin and Diaz-Jouanen[59]	*	*	*	*	*	*	*	*	8
Tsivgoulis et al.[56]		*	*	*	*	*	*	*	7
Pérez et al.[134]		*	*	*	*	*	*	*	7
Olea et al.[135]		*	*	*	*	*	*	*	7
Allinovi et al.[136]		*	*	*	*	*	*	*	7
Larochelle et al.[189]	*	*	*	*	*	*	*	*	8
Evans et al.[119]	*	*	*	*	*	*	*	*	8
Pawlitzki et al.[105]		*	*	*	*	*	*	*	7
Coraci et al.[106]		*	*	*	*	*	*	*	7
Pulicken et al.[95]	*	*	*	*	*	*	*	*	8
Tavakoli et al.[190]	*	*	*	*	*	*	*	*	8
Cicek et al.[48]		*	*	*	*	*	*	*	8
Kocer et al.[49]	*	*	*	*	*	*	*	*	8
Serarslan et al.[50]	*	*	*	*	*	*	*	*	8
Guijarro et al.[51]	*	*	*	*	*	*	*	*	8
Amaria et al.[131]		*	*	*	*	*	*	*	7
Fabi et al.[52]		*	*	*	*	*	*	*	7
Cortellini et al.[102]	*	*	*	*	*	*	*	*	8
Esme et al.[23]		*	*	*	*	*	*	*	7
Roskal-Walek et al.[191]		*	*	*	*	*	*	*	7
Niessen et al.[192]	*	*	*	*	*	*	*	*	8

Table 3. Quality assessment of case series

	Study				
	Baumgartner et al.[96]	**Rodrigues et al.[152]**	**Marco-Martin et al.[99]**	**Ball et al.[38]**	**Aviv et al.[55]**
Were there clear criteria for inclusion in the case series?	*	*	*	*	*
Was the condition measured in a standard, reliable way for all participants included in the case series?	*	*	*	*	*
Were valid methods used for identification of the condition for all participants included in the case series?	*	*	*	*	*
Did the case series have consecutive inclusion of participants?					*
Did the case series have complete inclusion of participants?					*
Were the demographics of the participants clearly reported in the study?	*	*	*	*	*
Were the clinical information of the participants clearly reported?	*	*	*		*
Were the outcomes or follow-up results of cases clearly reported?	*	*	*	*	*
Were the presenting site(s)/clinic(s) demographic information clearly reported?	*	*	*	*	*
Was the statistical analysis appropriate?					
Total score	7	7	7	6	9

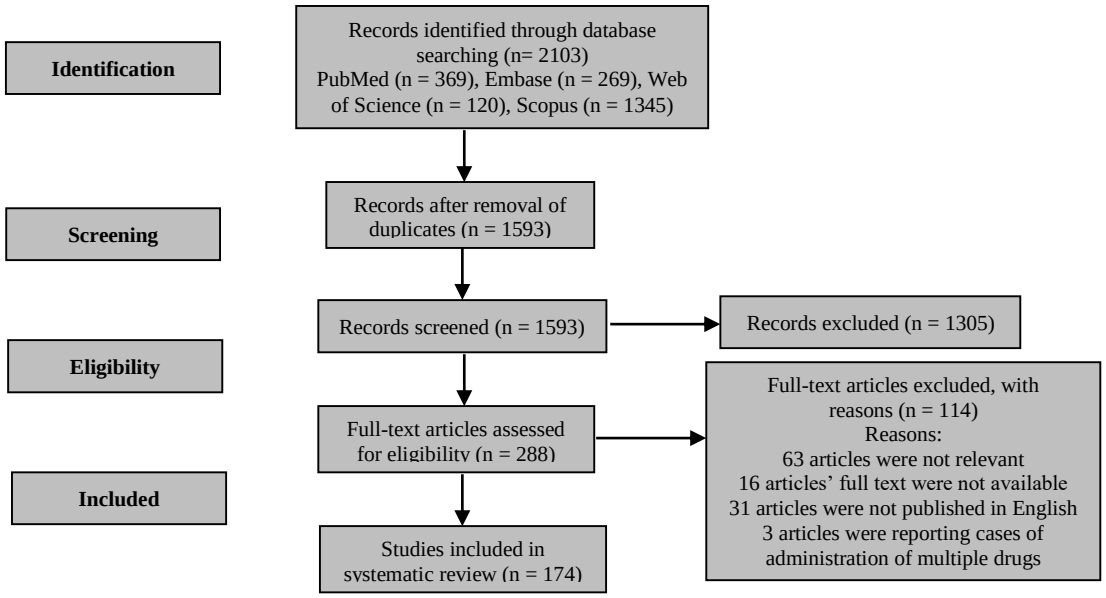

Figure 1. The flow chart of inclusion of studies

The quality score of case reports and case series were within the range of 6-8 (out of 8) and 6-9 (out of 10), respectively.

Discussion

In this article, we aimed to summarize the side effects of GA and IFN beta-1a, and to our knowledge, this is the first systematic review of case reports and case series in this field. An important point to consider in the treatment of MS is that due to the long-term administration of disease-modifying medications, there is a high possibility of incidence of acute or chronic side effects in the patients.

The reported side effects of IFN beta-1a and GA include numerous diseases and reactions. However, an important point was that a common factor in most adverse events was the effect of immune system disorders on the onset of side effects. In other words, most side effects are caused either by hypersensitivity or autoimmune responses, which y be related to the impact of GA and IFN beta-1a on the immune system.

Various mechanisms have been suggested for the side effects of GA and IFN beta-1a, which have mainly focused on immunomodulatory effects. GA can induce T cells to develop a T cell helper 2 (Th-2) pathway which has cross-reactivity with myelin basic protein (MBP).[15] Furthermore, Th-2 cells produce several cytokines including interleukin (IL)-4, IL-6, and IL-10 that contribute to the production of autoantibodies.[16] Therefore, administrating GA can have a significant association with autoimmune disorders, particularly in patients susceptible of developing autoimmune disease. Furthermore, Buttmann et al. have reported that subcutaneous injection of IFN beta triggers some local chemokine induction, which initiate skin inflammatory reactions.[17] However, some side effects such as Nicolau syndrome were associated with the injection itself rather immunological mechanisms.[18]

Our study had several limitations. First, several case reports and case series had limited information about the side effects. Furthermore, some causal relationships between drug administrations and side effects were not clear.

Future studies should aim to clarify the mechanism of GA and IFN beta-1a side effects in order to prevent or, at least, reduce the incidence of drug-associated adverse events. Second, as there is not a sufficient number of observational studies and RCTs that have assessed rare side effects, further studies should be performed to provide more information in this regard.

Conclusion

GA and IFN beta-1a, as disease-modifying therapy for patients with MS, are associated with a wide range of side effects. However, because of these adverse events should be further investigated in future interventional and observational studies.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

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