Dialogues in Clinical Neuroscience & Mental Health

DOI: 10.26386/obrela.v2i2.114 ISSN 2585-2795

Safety of the newer disease-modifying agents for multiple sclerosis: disproportionality analysis in the FDA Adverse Events Reporting System database.

Vasiliki Nikolopoulou, Spyridon Siafis, Antonios Milonas, Dimitrios Kouvelas, Georgios Papazisis
Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Greece.

Abstract

Purpose: Aim of the present study was to identify potential safety signals for the six newer disease-modifying therapies (DMTs) for multiple sclerosis using the FDA Adverse Events Reporting System (FAERS) database.

Methods: A case/non-case study was conducted with data from spontaneous reports submitted in FAERS between 2004 and 2018, using the OpenVigil2.1-MedDRA. Daclizumab, natalizumab integrin, alemtuzumab dimethyl fumarate, fingolimod, teriflunomide were examined. Adverse events were selected by the Summary Product Characteristics of the products, including all frequency levels. The reporting odds ratio (ROR) was used to express the association between DMTs and reporting adverse events.

Results: Currently approved DMTs share some common side effects such as increased risk for infections (especially progressive multifocal leukoencephalopathy and herpes virus infections), risk for neoplasms (basal and squamous cell carcinoma, kaposi's sarcoma) and blood disorders (lymphopenia, leukopenia, pure red cell aplasia) which were confirmed by our analysis.

Conclusion: This disproportionality analysis strengthens the already knowledge about the safety of DMTs for multiple sclerosis and emerges some new potential safety signals.

Keywords: multiple sclerosis, drug safety, disease-modifying therapies, FDA Adverse Events Reporting System

Special Issue in Demyelinating Diseases

Corresponding Author: Georgios Papazisis, Psychiatrist, Associate Professor of Clinical Pharmacology, Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Tel and Fax: +30 2310 999323, e-mail: papazisg@auth.gr

DOI: 10.26386/obrela.v2i2.114 ISSN 2585-2795

Introduction

Multiple sclerosis (MS) is a chronic disabling disorder of the central nervous system with autoimmune demyelinating and neurodegenerative components. Disease course is highly variable but it can be classified as relapse-remitting (in about 85% of the new-onset MS) and primary or secondary progressive [1]. Recent advances in understanding the pathogenetic mechanisms led to the development of treatment options aiming to modify and improve disease progression rather than simply ameliorating symptoms; these treatments are usually called disease-modifying therapies (DMTs) [1]. Evolution of DMTs started in early 2000s with the introduction IFN-β1b and was later expanded with the introduction of natalizumab, but available DMTS are mainly effective on the relapse-remitting pattern of MS [1]. A considerable number of DMTs with different efficacy and tolerability patterns is available, yet their mechanism of actions is not clearly understood. Drug choice should consider the benefit-risk ratio for each individual. Therefore, DMTs are usually classified as first-line (moderately effective, favorable safety profile) and second-line (highly effective, risk of more severe side effects) [2]. Accordingly, a recent network meta-analysis found that there are differences in the efficacy of DMTs; alemtuzumab, natalizumab and ocrelizumab were the most efficacious [3]. Older DMTs have a long list of possible adverse effects in the Summary of Product Characteristics (SPC), in contrast to newer DMTs with not well-studied long-term safety [2]. Long-term safety of a DMTs cannot be studied with RCTs, and as a result post-marketing studies are needed. Herein, safety signals for the six DMTs for multiple sclerosis were evaluated using the FDA Adverse Events Reporting System (FAERS) database.

Methods

Examined DMTs and adverse events

The Six newer DMTs were examined in this study, three monoclonal antibodies (daclizumab, natalizumab integrin, alemtuzumab) and three oral agents (dimethyl fumarate, fingolimod, teriflunomide). The very recently approved DMTs ocrelizumab and cladribrine, were not included, because their data were not accessible with OpenVigil, the software used to analyze FAERS data [4]. Adverse events of the DMTs were selected by the Summary Product Characteristics of the products, including all frequency levels. A long list of adverse events was investigated (Table 1).

Table 1. Investigated adverse events selected from SPC of DMTs. Preferred terms (PT) according to MedDRA version 17 were used whenever available, otherwise higher level terms were used.

System Organ Classes	Adverse events
infections and infestations	influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, sepsis, herpes viral infection, tinea versicolor, pneumonia, progressive multifocal leukoencephalopathy, cryptococcal infections, nasopharyngitis, conjunctivitis, cellulitis, herpes zoster
neoplasms	basal cell carcinoma, malignant melanoma, lymphoma, squamous cell carcinoma, kaposi's sarcoma, merkel cell carcinoma, lymphoproliferative disorders
blood and lymphatic system disorders	lymphopenia, leuckopenia, neutropenia, anemia, thrombocytopenia, peripheral oedema, red blood cell analyses abnormal, leukocytosis, coagulopathies, pancytopenia, thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy, pure red cell aplasia, agranulocytosis, haemolytic anaemia
endocrine disorders	hirsutism
immune system disorders	rash, anaphylaxis, angioedema, urticaria, hypersensitivity
psychiatric disorders	anxiety, depression, insomnia, confusion and disorientation, hallucination, mental disorders, nightmare, psychotic disorder
nervous system disorders	headache, paraesthesia, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia, peripheral neuropathy, dizziness, migraine, posterior reversible encephalopathy syndrome-PRES, tremor, seizures, encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, paralysis and paresis, amnesia, hypertonia, burning sensation, flushing
eye disorders	vision blurred, macular oedema, photophobia, cataract, blindness, optic neuropathy
ear and labyrinth disorders	tinnitus, hypoacusis, deafness neurosensory
cardiac disorders	palpitations, bradycardia, atrioventricular block, T-wave inversion, myocardial infraction, tachycardia, heart failures, ventricular arrhythmias, cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ventricular hypertrophy, pericardial effusion, torsades de pointes
vascular disorders	hypertension, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders, venous thrombosis, shock
respiratory thoracic and mediastinal disorders	interstitial lung disease, cough, dyspnea, pleural effusion, nasal congestion and inflammations, respiratory failures, asthma, acute respiratory distress syndrome, hypoxia
gastrointestinal disorders	diarrhoea, nausea, abdominal pain upper, vomiting, toothache, pancreatitis, stomatitis, abdominal pain, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, acute and chronic pancreatitis, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying, pancreatic pseudocyst, subileus, gastroenteritis, gastritis
hepatobiliary disorders	alanine aminotransferase increase, gamma-glutamyltransferase increase, aspartate aminotransferase increase, acute hepatitis, bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice, venoocclusive liver disease, hepatic artery thrombosis, hepatic failure, drug-induced liver injury

metabolism and nutrition disorders	dyslipidemia, diabetes mellitus, hyperglycaemic conditions, hyperkalaemia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia, dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia
skin and subcutaneous tissue disorders	alopecia, acne, severe skin disorders, nail disorders, eczema, pruritus, dermatitis, photosensitivity, toxic epidermal necrolysis-Lyell's syndrome, Stevens Johnson syndrome, erythema
musculoskeletal and connective tissue disorders	musculoskeletal pain, myalgia, arthralgia, back pain, muscle spasms, pain in extremity, mobility decreased
renal and urinary disorders	pollakiuria, renal impairment, nephropathy-BK virus, renal failure, nephropathy toxic, renal tubular necrosis, oliguria, haemolytic uraemic syndrome, anuria, cystitis haemorrhagic
reproductive system and breast disorders	menorrhagia, dysmenorrhea, uterine bleeding
general disorders and administration site conditions	pyrexia, pain and discomfort, asthenic conditions, oedema, influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, temperature intolerance, fall, ulcer, thirst, fat tissue increased
Investigations	weight decrease, neutrophil count decrease, white blood cell count decrease, neutrophil count decreased, blood creatine phosphokinase increased, blood triglycerides increased, liver function tests abnormal, weight increased, amylase increased, blood lactate dehydrogenase increased, echocardiogram abnormal, electrocardiogram QT prolonged, blood immunoglobulin M decreased, Blood immunoglobulin G decreased, albumin urine present
injury, poisoning and procedural complications	post-traumatic pain, infusion-related reactions

Case/non-case study

A case/non-case study was conducted with data from spontaneous reports submitted in FAERS between 2004 and 2018, using the OpenVigil2.1-MedDRA, an open pharmacovigilance data mining and analysis tool [4]. FAERS is consisting of individual safety reports mainly by consumers and health professionals from the United States, including administrative information, patient demographics, adverse events, information about drug therapy, patient outcomes and type of reporter [5]. In FAERS, adverse events are coded using the MedDRA ontology (version 17 is implemented in OpenVigil2.1-MedDRA). As cases adverse events were evaluated and they were primarily identified by Preferred Terms (PT), and if not available a higher level term was used. Reports with one or more of DMTs as suspected, interacting or concomitant were used to define exposure. In each analysis, all the other events were defined as non-cases and all other drugs as non-exposure. OpenVigil2.1-MedDRA operates only on cleaned FDA data, that is to say deleting most duplicates or reports with missing data [4].

Disproportionality analysis

The reporting odds ratio (ROR) was used to express the association between DMTs and reporting adverse events. ROR estimates the frequency of the examined adverse event co-reported with DMTs compared with all other drugs in the database. Disproportionality or safety signals were defined when the lower boundary of the 95% CI of ROR was greater than one and the number of reports was higher than three [5].

Results

The dataset contained 5791772 reports submitted in FAERS

between 2014 and 2018. Alemtuzumab (FDA approved 2001) was included in 4992, daclizumab (FDA approved 2016) in 1784, natalizumab (FDA approved 2004) in 103387, dimethyl fumarate (FDA approved 2013) in 53621, fingolimod (FDA approved 2010) in 21077 and teriflunomide (FDA approved 2012) in 12122 reports. Disproportionality signals are reported in Table 2.

Table 2. Safety signals identified for the association between co-reporting of a DMT and an adverse event. PML: progressive multifocal leuckoencephalopathy, BCC: basal cell carcinoma, SCC: squamous cell carcinoma , ARDS: acute respiratory distress syndrome, TTP: thrombotic thrombocytopenic purpura

Drug	Adverse event (ROR; 95% CI)
Alemtuzumab	Infections: PML (21.64; 15.87-29.5), herpes zoster (10.54; 8.74-12.71), herpes simplex (9; 5.58-14.51), sepsis (5.57; 4.67-6.64), urinary tract infection (3.25; 2.66-3.98), oral herpes (2.57; 1.38-4.79), pharyngitis (2.29; 1.03-5.11), cystitis (2.3; 1.41-3.76), viral gastroenteritis (2.11; 1-4.43), pneumonia (2.66; 2.27-3.11), conjunctivitis (3.38; 1.76-6.52), Neoplasms: lymphoproliferative disorder (20; 11.78-33.93), BCC (13.19; 9.53-18.26), SCC (13.47; 9.27-19.57), neuroendocrine carcinoma (10.59; 2.63-42.63), melanoma (6.45; 4.28-9.73), Kaposi's sarcoma (5.68; 2.13-15.17), lymphoma (4.32; 2.69-6.97), Blood: lymphopenia (48.66; 39.95-59.27), pure red cell aplasia (20.84; 13.38-32.45), TTP (17.67; 11.59-26.95), leukopenia (11.66; 9.66-14.06), neutropenia (7.84; 6.74-9.12), anaemia (1.88; 1.49-2.37), thrombocytopenia (7.2; 6.15-8.44), coagulopathy (2.79; 1.58-4.92), pancytopenia (11.14; 9.32-13.32), thrombotic microangiopathy (12.67; 8.05-19.93), agranulocytosis (4.37; 2.53-7.54), haemolytic anaemia (14.19; 10-20.13) Immune: rash (2.09; 1.8-2.43) Psychiatric and neurologic: PRES (8.39; 5.4-13.04), headache (1.73; 1.52-1.97), encephalopathy (2.43; 1.41-4.18), paresis (4.85; 1.56-15.09) Cardiac: bradycardia (5.61; 4.43-7.11), tachycardia (3.06; 2.38-3.93), pericardial effusion (3.25; 1.99-5.32)

	Respiratory: ARDS (6.65; 4.55-9.72), respiratory failure (5.21; 4.23-6.42), pleural effusion (4.85; 3.8-6.2), intersistital lung disease (3.28; 2.27-4.72), cough (1.71; 1.37-2.13), dyspnea (1.27; 1.08-1.49), hypoxia (4.06; 2.78-5.93) Gastrointestinal and hepatobiliary disorders: venoocclusive liver disease (30.6; 21.27-44.02), hepatic artery thrombosis (13.97; 1.94-100.36), ascites (8.45; 6.43-11.12), ulcer (4.59; 1.48-14.27), gastroenteritis (4.06; 2.3-7.17) , ALT increased (4.51; 3.56-5.71), AST increased (2.76; 2-3.8), GGT increased (2.26; 1.28-3.98), acute hepatitis (2.73; 1.02-7.28), cholestasis (3.67; 2.03-6.64), jaundice (2.05; 1.56-3.36), hepatic failure (4.41; 3.19-6.1) Metabolic: fluid overload (4.37; 2.58-7.38), hyperglycaemia (2.05; 1.27-3.31), Skin: eczema (2.39; 1.24-4.6), erythema (1.37; 1.02-1.83) Renal: BK-virus infection (120.21; 86.36-167.35), cystitis haemorrhagic (27.38; 17.56-42.7), tubular necrosis (5.29; 2.84-9.86), renal impairment (2.25; 1.61-3.13), renal failure (2.52; 2.02-3.14), anuria (3.6; 1.8-7.22), General: pyrexia (5.91; 5.33-6.55), temperature intolerance (2.51; 1.04-6.03), neutrophil count decrease (4.91; 3.46-6.95), LDH decrease (4.85; 3.09-7.62), infusion related reaction (4.79; 3.51-6.55), liver function test abnormal (2.12; 1.41-3.2),
Daclizumab	Infections: urinary tract infection (7.3; 5.8-9.19), pharyngitis (3.21; 1.03-9.96), herpes zoster (4.35; 2.7-7.01), influenza (2.64; 1.66-4.21), upper tract infection (2.18; 1.04-4.59), cystitis (2.41; 1.08-5.38), herpes simplex (4.41; 1.42-13.7), sepsis (6.91; 5.31-9.01), pneumonia (1.73; 1.26-2.39),
	Neoplasms: lymphoproliferative disorder (11.82; 3.8-36.76), BCC (4.92; 2.04-11.84), SCC (12.02; 6.24-23.17), Kaposi's sarcoma (15.92; 5.96-42.58), Blood: pure red cell aplasia (40.77; 24.02-69.21), TTP (4.42; 1.1-17.71), lymphopenia (3.67; 1.18-11.4), leukopenia (3.38; 1.92-5.97), pancytopenia (3.65; 2.2-6.07), agranulocytosis (3.75; 1.41-10.02) Psychiatric and neurologic: optic neuropathy (15.55; 5-48.4), confusional state (2.49; 1.78-3.48), amnesia (2.28; 1.4-3.74), Vascular: hypertension (1.64; 1.12-2.4) Respiratory: ARDS (4.11; 1.84-9.17) Gastrointestinal and hepatobillary disorders: obstructive bile duct disorders (excluding neoplasms; 5.04; 1.62-15.67), impaired gastric emptying (5.76; 1.85-17.9), diarrhea (1.52; 1.18-1.94), ascites (3.15; 1.5-6.61), gastroenteritis (6.64; 3.16-13.95), ALT increased (2.5; 1.48-4.23), AST increased (3.05; 1.83-5.06), GGT increased (2.63; 1.09-6.34), Metabolic: fluid overload (6.99; 3.49-14), metabolic acidosis (4.36; 2.41-7.89), hyperglycaemia (3.04; 1.58-5.86), dehydration (2.5; 1.69-3.72) Skin: eczema (6.71; 3.48-12.93), photosensitivity reaction (6.22; 3.23-11.98), dermatitis (4.74; 1.97-11.41), Muscle: mobility decreased (5.13; 3.48-7.56) Renal: BK-infection (63.61; 31.55-128.25), tubular necrosis (19.39; 11.22-33.52), HUS (12.22; 3.93-38.01), toxic nephropathy (7.9; 3.54-17.62), anuria (5.04; 1.89-13.45) renal impairment (2.15; 1.22-3.8),

	General: temperature intolerance (5.62; 2.1-15), liver function test abnormal (4.94; 3.14-7.77), influenza-like illness (2.83; 1.91-4.2), LDH increased (2.85; 1.07-7.59), fall (1.5; 1.08-2.09), pyrexia (1.61; 1.18-2.19)
Natalizumab	Infections: influenza (3.14; 2.96-3.33), upper tract infection (2.7; 2.46-2.95), urinary tract infection (6.36; 6.14-6.59), bronchitis (2.79; 2.61-2.99), sinusitis (3.56; 3.37-3.76), pharyngitis (1.54; 1.24-1.92), cystitis (6.96; 6.49-7.46), viral gastroenteritis (4.23; 3.74-4.78), oral herpes (2.11; 1.81-2.47), tooth infection (3.24; 2.75-3.81), laryngitis (2.19; 1.8-2.66), tinea pedis (2.42; 1.51-3.87), PML (29.6; 27.13-32.28), nasopharyngitis (196.04; 191.6-200.58), cellulitis (1.52; 1.36-1.69), herpes zoster (4.35; 4.07-4.65) Neoplasms: BCC (1.61; 1.31-1.97), melanoma (1.81; 1.53-2.15) Immune: hypersensitivity (1.94; 1.85-2.04) Psychiatric and neurologic: migraine (2.89; 2.71-3.07), headache (2.25; 2.19-2.31), amnesia (2.06; 1.92-2.21), depression (1.39; 1.33-1.45), confusional state (1.43; 1.35-1.52), paraesthesia (1.92; 1.83-2.02), sciatica (1.78; 1.43-2.21), carpal tunnel syndrome (1.38; 1.43-2.21), hyperesthesia (1.7; 1.35-2.14), neuralgia (1.7; 1.35-2.14), tremor (1.77; 1.68-1.86), seizures (1.15; 1.09-1.22), paralysis (1.29; 1.07-1.56), burning sensation (1.51; 1.38-1.64) Eye: vision blurred (1.5; 1.4-1.59), blindness (1.31; 1.16-1.48) Ear: hypoacusis (1.48; 1.32-1.66) Gastrointestinal and hepatobillary disorders: toothache (1.62; 1.36-1.93)
	Muscle: mobility decreased (8.71; 8.32-9.11)musculoskeletal pain (1.3; 1.18-1.44), arthralgia (1.16; 1.1-1.21), back pain (1.52; 1.45-1.6), pain in extremity (2.24; 2.16-2.33), Renal: pollakiuria (1.18; 11.04-1.35) General: temperature intolerance (16.26; 14.75-17.92), fall (3.35; 3.25-3.46), infusion-related reaction (3.27; 3-3.57), post-traumatic pain (2.75; 1.01-7.51), discomfort (2.05; 1.87-2.24), influenza-like illness (1.91; 1.79-2.04), pain (1.27; 1.23-1.32), feeling abnormal (1.23; 1.17-1.29), pyrexia (1.12; 1.06-1.17),

Dimethyl fumarate	Infections: viral gastroenteritis (2.5; 2.02-3.09), herpes zoster (2.41; 2.14-2.71), urinary tract infection (2.04; 1.89-2.21), influenza (1.89; 1.71-2.09), cystitis (1.87; 1.58-2.2), PML (1.74; 1.25-2.41), nasopharyngitis (1.76; 1.63-1.9), Blood: lymphopenia (5.24; 4.38-6.28) Immune: rash (1.08; 1.01-1.15), hypersensitivity (1.26; 1.16-1.37) Psychiatric and neurologic: flushing (31; 30.16-31.88), burning sensation (4.18; 3.89-4.49), paraesthesia (2.29; 2.14-2.43), neuralgia (2.09; 1.72-2.54), amnesia (1.89; 1.71-2.09), confusional state (1.69; 1.57-1.82), headache (1.32; 1.26-1.38), migraine (1.68; 1.51-1.87), Eye: blindness (2.06; 1.8-2.36) Ear: hypoacusis (2.07; 1.81-2.37) Gastrointestinal and hepatobillary disorders: abdominal pain upper (5.18; 4.96-5.41), diarrhea (2.71; 2.62-2.81), nausea (2; 1.93-2.07), vomiting (2.15; 2.06-2.24), abdominal pain (1.56; 1.46-1.67), dyspepsia (2.45; 2.25-2.65), flatulence (2.69; 2.42-2.98), constipation (1.49; 1.38-1.62), GERD (1.25; 1.1-1.42)
	Metabolic: dehydration (1.3; 1.17-1.44) Skin: pruritus (2.9; 2.77-3.04), erythema (2.68; 2.51-2.86), alopecia (2.3; 2.17-2.45), Muscle: mobility decreased (4.74; 4.39-5.12) General: temperature introlerance (4.63; 3.77-5.68), influenza-like illness (1.8; 1.65-1.97), feeling abnormal (1.17; 1.09-1.26), fall (1.6; 1.51-1.7)
Fingolimod	Infections: herpes zoster (6.93; 6.18-7.76), PML (6.86; 5.25-8.97), nasopharyngitis (2.92; 2.65-3.22), urinary tract infection (2.49; 2.3-2.79), influenza (2.03; 1.74-2.37), upper tract infection (2.58; 2.11-3.15), oral herpes (2.02; 1.43-2.84), herpes simplex (2.12; 1.31-3.42), laryngitis (2.13; 1.39-3.27), bronchitis (1.98; 1.66-2.36), sinusitis (1.87; 1.59-2.2), cystitis (2.05; 1.59-2.64), viral gastroenteritis (1.86; 1.26-2.73), conjunctivitis (1.69; 1.08-2.66), Neoplasms: BCC (7.15; 5.76-8.88), melanoma (4.21; 3.28-5.4), SCC (2.37; 1.54-3.64) Blood: lymphopenia (21.01; 18.1-24.38), leukopenia (2.51; 2.07-3.04) Psychiatric and neurologic: paresis (8.64; 5.65-13.21), migraine (2.88; 2.52-3.29), headache (2.38; 2.25-2.51), paraesthesia (2.48; 2.26-2.74), depression (1.39; 1.26-1.54), confusional state (1.73; 1.54-1.94), neuralgia (3.49; 2.74-4.44), dizziness (2.08; 1.95-2.22), tremor (1.31; 1.16-1.49), seizures (1.53; 1.37-1.71), paralysis (1.6; 1.11-2.33), amnesia (1.67; 1.41-1.97), hypertonia (1.87; 1.2-2.9), burning sensation (1.32; 1.08-1.61) Eye: macular oedema (46.58; 40.81-53.15), vision blurred (4.25; 3.91-4.63), photobia (3.44; 2.63-4.5), blindness (2.29; 1.87-2.8), cataract (1.31; 1.01-1.71),

	Cardiac: T wave inversion (9; 6.14-13.21), bradycardia (5.08; 4.49-5.74), atrioventricular block (2.8; 1.87-4.18), palpitations (2.32; 2.07-2.61), Vascular: hypertension (1.2; 1.05-1.36) Respiratory: cough (1.97; 1.78-2.17), dyspnea (1.26; 1.16-1.36) Gastrointestinal and hepatobillary disorders: γ-GT increased (4.38; 3.58-5.36) ALT increased (2.68; 2.31-3.11), AST increased (1.99; 1.66-2.39), nausea (1.15; 1.07-1.23), Skin: alopecia (1.46; 1.29-1.64) Muscle: back pain (2.55; 2.34-2.78), musculosketal pain (1.25; 1-1.56), pain in extremity (1.52; 1.39-1.67), mobility decreased (1.89; 1.57-2.27) Renal: pollakiuria (1.68; 1.32-2.14) General: temperature intolerance (6.17; 4.67-8.15), blood IgG decreased (5.5; 2.45-12.33), QT prolonged (2.28; 1.84-2.83), feeling abnormal (2.03; 1.86-2.22), fall (2.09; 1.93-2.27), influenza-like illness (1.95; 1.7-2.24), liver function test abnormal (2.2; 1.8-2.67), pain (1.09; 1-1.18), discomfort (1.48; 1.18-1.86), pyrexia (1.38; 1.25-1.52),
Teriflunomide	Infections: cystitis (3.7; 2.88-4.75), urinary tract infection (3.35; 2.95-3.81), viral gastroenteritis (2.61; 1.7-4.01), bronchitis (2.08; 1.66-2.6), laryngitis (2.11; 1.2-3.72), nasopharyngitis (2.06; 1.77-2.39), influenza (1.94; 1.58-2.39), herpes zoster (1.95; 1.48-2.56), sinusitis (1.46; 1.15-1.85) Blood: lymphopenia (3.98; 2.62-6.06) Immune: rash (1.65; 1.49-1.84)

	Psychiatric and neurologic: paraesthesia (7.11; 6.57-7.69), neuralgia (4.62; 3.5-6.09), burning sensation (3.77; 3.22-4.4), carpal tunnel syndrome (2.75; 1.75-4.31), peripheral neuropathy (2.66; 2.21-3.19), paralysis (2.29; 1.52-3.46),headache (2.23; 2.07-2.4), sciatica (2.12; 1.2-3.74), dizziness (1.18; 1.06-1.31), migraine (1.94; 1.57-2.4), depression (2.18; 1.96-2.43), insomnia (1.16; 1-1.33), Eye: blindness (1.69; 1.24-2.3)vision blurred (1.54; 1.29-1.84), Respiratory: cough (1.33; 1.14-1.56) Gastrointestinal and hepatobillary disorders: diarrhea (5.26; 4.97-5.56), abdominal pain upper (1.94; 1.69-2.23), nausea (1.89; 1.76-2.03), pancreatitis (1.99; 1.61-2.47), flatulence (1.47; 1.1-1.96), ALT increased (1.79; 1.41-2.27), hepatocellular injury (1.73; 1.02-2.93) Metabolic: decreased appetite (1.46; 1.25-1.7) Skin: mobility decreased (4.34; 3.69-5.11) back pain (1.72; 1.5-1.96), alopecia (1.35; 1.02-1.78), pain in extremity (2.13; 1.92-2.37), Renal: pollakiuria (2.7; 2.1-3.48) General: temperature abnormal (8.18; 5.96-11.23), fall (3.87; 3.57-4.2), pain (1.58; 1.44-1.72), influenza-like illness (2.08; 1.74-2.48), weight decreased τ(2.1; 1.87-2.37), liver function test abnormal (1.9; 1.44-2.51), feeling abnormal (1.57; 1.38-1.79), discomfort (1.46; 1.08-1.97)

Interestingly, although alemtuzumab was included in a smaller number of reports compared to the most of the other agents our analysis revealed significantly more safety signals with a higher ROR (>5). Particularly, alemtuzumab was significantly associated with various types of infections, with the strongest signal identified for bk polyomavirus infection (ROR 120.21; 95% CI 86.36-167.35), progressive multifocal leukoencephalopathy and herpes virus infections. Potential safety signals also emerged for blood disorders (lymphopenia, pure red cell aplasia, thrombotic thrombocytopenic purpura, haemolytic anaemia, leukopenia) but also neoplasms (lymphoproliferative disorder, basal cell carcinoma, squamous cell carcinoma. Venoocclusive liver disease and cystitis haemorrhagic were also significantly associated with alemtuzumab. Similar to alemtuzumab, the statistically strongest signal for daclizumab emerged for bk polyomavirus infections (ROR 63.61; 95% CI 31.55-128.25). Potential signals from the renal system included tubular necrosis and urinary tract infection. Further, the analyses showed significant association between daclizumab exposure and neoplasms (squamous cell carcinoma and Kaposi's sarcoma). Pure red cell aplasia was also strongly associated with daclizumab use. According to the analysis, the most probable safety signal for natalizumab was for nasopharyngitis (ROR 196.04; 95% CI 191.6-200.58). Progressive multifocal leukoencephalopathy, cystitis, urinary tract infection and herpes zoster infection were also identified as potential safety signals.

Dimethyl fumarate revealed a different adverse event profile since potential safety signals emerged for flushing, upper abdominal pain, decreased muscle mobility, lymphopenia, burning sensation and temperature intolerance. The most significant association for fingolimod was found for eye macular oedema (ROR 46.58; 40.81-53.15), followed by lymphopenia and herpes zoster infection. Electrocardiogram t wave inversion, basal cell carcinoma and progressive multifocal leukoencephalopathy were also significantly associated with fin-

golimod use. Finally, teriflunamide exposure was significantly associated with alopecia, nervous system paraesthesia, temperature intolerance and diarrhea.

Discussion

The safety profile of DMTs for multiple sclerosis has been evaluated using disproportionality analysis in the large pharmacovigilance database of FDA. Currently approved DMTs have different mechanisms of actions on targeting the immune system, therefore, they have different side effect profiles [6]. However, they share some common side effects such as increased risk for infections (e.g progressive multifocal leukoencephalopathy, herpes virus infections), risk for neoplasms (basal and squamous cell carcinoma, kaposi's sarcoma) and blood disorders (e.g lymphopenia, leukopenia, pure red cell aplasia, haemolytic anaemia) which were confirmed by our analysis.

The first disease-modifying treatment approved were IFN beta and glatiramer acetate, while the first approved newer agent with a different mechanism of action was natalizumab in 2004. Natalizumab, an anti-4alpha integrin monoclonal antibody, was temporarily suspended in 2005 after the reporting of 3 cases with progressive multifocal leucoencephalopathy in clinical trials. After the implementation of TOUCH safety recording system, for the early detection of PML, natalizumab was re-approved in 2006. Globally recording systems were developed by the marketing authorization holder to follow up infections, malignancies, melanoma and other adverse events occurring under natalizumab treatment (Tysabri Global Observational Program in Safety [TYGRIS], Tysabri Observational Protocol [TOP]) [7-9]. Our analysis confirmed the safety signal for PML and other infections, especially cystitis, urinary tract infection and herpes zoster infection. The strongest association for natalizumab use was found for nasopharyngitis.

Alemtuzumab is a humanized monoclonal antibody which binds to CD52, expressed by T and B lymphocytes, monocytes, macrophages, and eosinophils. It has the longest lasting effect on immune system among drugs used for MS. Our disproportionality analysis showed significant associations between alemtuzumab exposure and various types of infections, with the strongest signal identified for bk polyomavirus infection, progressive multifocal leukoencephalopathy and herpes virus infections. Potential safety signals also emerged for blood disorders (lymphopenia, pure red cell aplasia, thrombotic thrombocytopenic purpura, haemolytic anaemia, leukopenia) but also neoplasms (lymphoproliferative disorder, basal cell carcinoma, squamous cell carcinoma. Our findings strengthen the results of previous alemtuzumab trials that recorded mainly mild infections, but also serious opportunistic infections such as listeria meningitis or CMV activation. Secondary autoimmunity. have also been reported, including thyroid related disorders, immune mediated thrombocytopenia and rare cases of autoimmune nephropathies [10]. Those findings led to the development of a safety vigilance program to monitor any autoimmune disorders, renal, thyroid and hematological functions are screened regularly for the first 48 months after treatment [11].

Daclizumab is an anti-IL-2 monoclonal antibody, which received warning about hepatic injury and immune-mediated disorders. In addition the SPC warned about hypersensitivity reactions, depression, infections (such as upper respiratory tract infections and nasopharyngitis) [12]. To our results, statistically safety signal emerged for bk polyomavirus infections, pure red cell aplasia tubular necrosis, urinary tract and neoplasms (squamous cell carcinoma and kaposi's sarcoma). However, in March 2018, the drug was immediately suspended from the market after 12 reports of serious inflammatory brain encephalitis and meningoencephalitis with three of the cases being fatal [13].

The first oral agent approved for MS was fingolimod in 2010, a sphingosine 1 phosphate (S1P) analogue. In our analysis the most significant association for fingolimod was found for eye macular oedema followed by lymphopenia, herpes zoster infection, electrocardiogram t wave inversion, basal cell carcinoma and progressive multifocal leukoencephalopathy. Secondary macular edema due to retinal S1P receptor modulation leading to increased vascular permeability, has been reported in 0.5% of patients receiving 0.5 mg fingolimod in the clinical trials. Regulators require ophthalmological exam before initi-

ation of fingolimod treatment and because macular edema is most prevalent in the first 3–4 months after treatment onset, ophthalmological examination should be repeated at that time. Fingolimod should be stopped in the case of macular edema [14].

Teriflunomide is the second oral medication approved by FDA for the treatment of MS in 2012. In the clinical trials, most common side effects were headache, liver enzyme abnormalities, diarrhea, alopecia and nausea. Alopecia is usually mild and usually recovers after the first months [15]. Our results confirmed that, the most significant association for teriflunamide exposure was for alopecia, followed by nervous system paraesthesia, temperature intolerance and diarrhea.

Finally, the third oral drug approved 2013 for MS is dimethyl fumarate. It is a first-line drug with immunomodulatory and cytoprotective effects. According to the pre-marketing trial the most common adverse effects included flushing, abdominal pain, diarrhea, nausea, vomiting, pruritus and papular eruption [16]. In accordance, our analysis revealed potential safety signals for flushing, upper abdominal pain, decreased muscle mobility, lymphopenia, burning sensation and temperature intolerance.

The strengths of our analysis are the large number of reports and the comprehensive list of adverse events. However, it has certain limitations. First, the older disease-modifying agents IFN-β and glatiramer acetate were not investigated, yet they have quite well-known safety profile. Second, pharmacovigilance databases suffer from under-reporting, temporal patterns of reporting, notoriety of the adverse event and suboptimal quality of reports [5]. In addition, all other drugs in FAERs were used as reference in the disproportionality analysis as well as indication bias could have infiltrated the results. Finally, disproportionality analysis is a statistical method that measures co-reporting of adverse events and drugs, without being able to confirm causality.

Concluding, this disproportionality analysis strengthens the already knowledge about the safety of DMTs for multiple sclerosis and emerges some new potential safety signals. Considering the limitations of pharmacovigilance databases and statistical analysis, an appropriate causality assessment is needed to validate these signals, while further research is warranted to elucidate the comparative safety profile of DMTs in MS.

References

1. Ransohoff, R.M., D.A. Hafler, and C.F. Lucchinetti, Multiple sclerosis-a quiet revolution. Nature reviews. Neurology, 2015. 11(3): p. 134-142. doi: 10.1038/nrneurol.2015.14.

2. Soelberg Sorensen, P., Safety concerns and risk management of multiple sclerosis therapies. Acta Neurol Scand, 2017. 136(3): p. 168-186. doi: 10.1111/ane.12712.

3. Lucchetta, R.C., et al., Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis: A Network Meta-Analysis. CNS Drugs, 2018. 32(9): p. 813-826. doi: 10.1007/s40263-018-0541-5

4. Böhm, R., et al., OpenVigil FDA – Inspection of U.S. American Adverse Drug Events Pharmacovigilance Data and Novel Clinical Applications. PLOS ONE, 2016. 11(6): p. e0157753. doi.org/10.1371/journal.pone.0157753

5. Sakaeda, T., et al., Data mining of the public version of the FDA Adverse Event Reporting System. Int J Med Sci, 2013. 10(7): p. 796-803. doi: 10.7150/ijms.6048

6. TaŞKapilioĞLu, Ö., Recent Advances in the Treatment for Multiple Sclerosis; Current New Drugs Specific for Multiple Sclerosis. Noro psikiyatri arsivi, 2018. 55(Suppl 1): p. S15-S20. doi: 10.29399/npa.23402

7. Selewski, D.T., et al., Natalizumab (Tysabri). American Journal of Neuroradiology, 2010. 31(9): p. 1588. DOI: https://doi.org/10.3174/ajnr.A2226

8. Sabol, R.A., et al., Melanoma complicating treatment with natalizumab for multiple sclerosis: A report from the Southern Network on Adverse Reactions (SONAR). Cancer Med, 2017. 6(7): p. 1541-1551. doi: 10.1002/cam4.1098

9. FDA, TYSABRI® (natalizumab) Injection FULL PRESCRIBING INFORMATION 2018.

10. Guarnera, C., P. Bramanti, and E. Mazzon, Alemtuzumab: a review of efficacy and risks in the treatment of relapsing remitting multiple sclerosis. Ther Clin Risk Manag, 2017. 13: p. 871-879. doi: 10.2147/TCRM

11. Devonshire, V., et al., Monitoring and management of autoimmunity in multiple sclerosis patients treated with alemtuzumab: practical recommendations. J Neurol, 2018. 265(11): p. 2494-2505. DOI: 10.1007/s00415-018-8822-y

12. FDA, ZINBRYTA (daclizumab) injection, for subcutaneous use 2017.

13. EMA. EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta. 2018 [cited 2018 07/03/2018]; Available from: https://www.ema.europa.eu/en/news/ema-recommends-immediate-suspension-recall-multiple-sclerosis-medicine-zinbryta.

14. Eckstein, C. and M.T. Bhatti, Currently approved and emerging oral therapies in multiple sclerosis: An update for the ophthalmologist. Surv Ophthalmol, 2016. 61(3): p. 318-32. DOI: 10.1016/j.survophthal.2015.12.001

15. Confavreux, C., et al., Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol, 2014. 13(3): p. 247-56. DOI:

10.1016/S1474-4422(13)70308-9

16. Fox, R.J., et al., Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med, 2012. 367(12): p. 1087-97. DOI: 10.1056/NEJMoa1206328