CASE REPORT

Immune thrombocytopenic purpura associated with fingolimod

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SUMMARY

Fingolimod is an oral sphingosine-1-phosphate receptor modulator which causes lymphocyte sequestration in lymph nodes and is approved for relapsing multiple sclerosis. The Therapeutic Goods Administration of Australia is aware of only one case where fingolimod preceded immune thrombocytopenic purpura (ITP) by 5 weeks. Here we report three such cases.

None were on any medications known to cause ITP and routine investigations were unremarkable. All cases were treated with immunosuppression. Case 1 successfully weaned prednisolone after fingolimod cessation whereas case 2 weaned slowly while continuing fingolimod therapy. Case 3 had more refractory ITP and re-exposure to fingolimod worsened thrombocytopenia.

There was a temporal association between fingolimod exposure and ITP however dose–effect association and pathogenesis remain less clear.

In conclusion, our cases highlight that clinicians should be aware of the possible association between ITP and fingolimod.

BACKGROUND

Fingolimod (FTY720) is an oral sphingosine-1-phosphate receptor (S1pr) modulator which alters lymphocyte migration causing their sequestration in lymph nodes.[1] It was approved in September 2010 by US Food and Drug Administration for relapsing forms of multiple sclerosis (MS) following evidence it reduced relapse rates by 50%.[2 3] Known side effects of fingolimod include increased rates of infections such as varicella zoster and more recently reports of progressive multifocal leukoencephalopathy,[4] macular oedema, bradycardia and lymphopenia.[2 3]

A post market report from European Medicines in April 2014 highlighted a possible association between fingolimod and thrombocytopenia. They noted 115 cases including 7 cases of immune thrombocytopenic purpura (ITP) over a 5-month period,[5] much higher than the expected background incidence of 3 per 100 000 adults.[6] Interestingly 11 cases of thrombocytopenia had resolution on fingolimod cessation and 1 case relapsed on re-exposure raising the possibility of causality. The Therapeutic Goods Administration of Australia as of September 2015 were aware of only one case where fingolimod preceded ITP by 5 weeks however further details were unable to be disclosed.

At our institution, approximately 300 patients are treated with fingolimod. Here, we report three cases of ITP associated with fingolimod therapy with more details available in tables 1-4.

CASE PRESENTATION

Case 1

A 22-year-old woman was admitted for severe thrombocytopenia having noticed bruising and a petechial rash. She had a history of relapsing remitting MS diagnosed 2 years prior when she presented with optic neuritis and had been on fingolimod for 12 months. She was on 0.5 mg alternate daily due to lymphopenia of 0.2×10^9/L without anaemia.

Apart from easy bruising, she denied any bleeding and had no recent illnesses. Her only other medication was levonorgestrol–ethinyloestradiol.

Physical examination was notable only for mild petechiae and purpura.

Case 2

A 59-year-old woman was admitted for severe thrombocytopenia having had spontaneous bruising for 2 weeks. Her history was significant for MS diagnosed 2 years prior when she presented with optic neuritis. She subsequently presented with dysarthria and unilateral weakness and MRI showed further demyelination. With lymphopenia of 0.5×10^9/L and neutrophils of 1.3×10^9/L on interferon beta-1a, she had been switched to fingolimod 0.5 mg daily 8 weeks prior.

Her history was significant for rheumatoid arthritis, which was stable on hydroxychloroquine 200 mg two times per day, and Graves' disease.

Her other medications were krill oil, glucosamine and calcium supplements.

She had no recent illnesses and physical examination was unremarkable apart from bruising.

Case 3

A 51-year-old woman presented with a platelet count of 23×10^9/L after she noticed easy bruising. She was diagnosed 20 years prior with MS when she presented with left-sided haemiparesis. She had started fingolimod 0.5 mg daily 19 months prior and this had been ceased the day prior on discovery of thrombocytopenia. Her only other medication was ethinyloestradiol–levonorgestrel.

She had no antecedent infections and examination was unremarkable apart from bruising.

OUTCOME AND FOLLOW-UP

Case 1

Case 1 commenced on prednisolone 1 mg/kg daily and her fingolimod was continued as per her neurologist.

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Table 1 Case demographics and other parameters

	Case 1	Case 2	Case 3
Year at ITP diagnosis	2014	2013	2014
Age (years)	22	59	51
Sex	F	F	F
MS duration (years)	3	2	10
MS course	2012: right optic neuritis with MRI brain: T2 frontal white matter lesion 2013: MRI brain: new T2 lesion 2013: right optic neuritis	2011 July: left optic neuritis with MRI brain: equivocal cerebral peduncle T2 lesion only 2011 September: right-sided weakness and dysarthria MRI brain: supra and infratentorial T2 lesions	1994: left-sided weakness and spasticity Imaging studies not available 1997: relapse of left-sided weakness and spasticity
Previous MS therapy	2013: dimethyl fumarate→ lymphopenia requiring cessation 2014	October 2011: beta interferon → persistent lymphopenia and neutropenia prompting cessation 2012–2013	1997: beta interferon
Other autoimmune conditions	–	Rheumatoid arthritis Graves' disease	–
Autoimmune testing/*H. pylori* screening	Negative	Negative	Negative
Viral screening at initial presentation (HBV, HCV, HIV, CMV, EBV)	Negative	Negative	Negative
Protein electrophoresis	Negative	Negative	Negative
Evidence of splenomegaly	None clinically	None clinically	None clinically
Bone marrow biopsy	Not undertaken	Not undertaken	June 2014: normal trilineage haematopoiesis with plentiful megakaryocytes
Duration of fingolimod prior to ITP	12 months	2 months	19 months
Fingolimod dose	0.5 mg alternate daily	0.5 mg daily	0.5 mg daily
Fingolimod post thrombocytopenia	Continued	Continued	Discontinued
ITP treatment	Prednisolone	Prednisolone IVIg azathioprine hydroxychloroquine	Prednisolone IVIg azathioprine hydroxychloroquine Eltrombopag Romiplostim
Time to CR (months)	0.4	2.5	0.2
ITP relapses (Plt $<30\times10^9$/L)	Nil	Nil	Five (one precipitated by fingolimod reinitiation)
Duration of ITP treatment (months)	6.7	25.2	15.7 (ongoing)

CMV, cytomegalovirus; CR, complete remission; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; *H. pylori*, *Helicobacter pylori*; ITP, immune thrombocytopenic purpura; MS, multiple sclerosis; Plt, platelets.

Table 2 Case 1 Full blood counts, fingolimod and ITP management

Date	Haemoglobin (g/L)	White cell count ($\times10^9$)	Platelet count ($\times10^9$)	Fingolimod dose	Prednisolone (mg daily)
11/10/2013	119	5.6	298		
14/04/2014	116	6	294		
19/05/2014	116	4.7	263		
15/06/2014	NA	NA	NA	0.5 mg alternate daily	
9/07/2014	117	5.1	288	0.5 mg alternate daily	
31/10/2014	126	5.7	367	0.5 mg alternate daily	
13/02/2015	128	5.3	277	0.5 mg alternate daily	
9/07/2015	121	4.8	12	0.5 mg alternate daily	50
13/07/2015	114	7	51	0.5 mg alternate daily	37.5
20/07/2015	125	8.8	490	0.5 mg alternate daily	25
27/07/2015	119	5.9	202	0.5 mg alternate daily	20
3/08/2015	135	5.7	260	Ceased	15
10/8/2015	139	4.5	273		10
2/09/2015	145	9.5	201		Ceased
2/02/2016	152	8.1	399		

ITP, immune thrombocytopenic purpura.

Her platelet count rose to $>50\times10^9$/L within a week. Prednisolone was subsequently tapered to cease 1 month later with normalisation of her platelet counts.

While on a weaning dose of prednisolone, her neurologist ceased her fingolimod because MRI revealed two small new brain lesions reflecting treatment failure. She was subsequently

Table 3 Case 2 Full blood counts, fingolimod and ITP management

Date	Haemoglobin (g/L)	White cell count ($\times 10^9$)	Platelet count ($\times 10^9$)	Prednisolone dose (mg daily)	Fingolimod dose (mg daily)	IVIg (g)	Azathioprine (mg daily)	Hydroxychloroquine (mg daily)
9/02/2013	133	2.2	110					400
21/03/2013	125	2.5	122					400
8/05/2013	NA	NA	NA		0.5			400
25/05/2013	124	1.8	56		0.5			400
24/07/2013	115	2.6	1	75	0.5	85		400
27/07/2013	108	2.3	15	75	0.5			400
28/07/2013	109	2.4	29	75	0.5			400
8/08/2013	126	5.4	9	75	0.5	90		400
14/08/2013	126	4.5	97	75	0.5			400
22/08/2013	129	4.4	38	75	0.5			600
27/08/2013	123	3.1	21	75	0.5		100	400
3/09/2013	126	4.2	47	50	0.5		150	400
17/09/2015	123	4.2	65	37.5	0.5		150	400
1/10/2013	119	3.7	95	25	0.5		150	400
8/10/2013	123	2.5	110	12.5	0.5		150	400
4/11/2013	133	2.2	91	Ceased	0.5		150	400
26/11/2013	131	2.2	117		0.5		150	400
3/04/2014	131	1.9	135		0.5		150	400
3/07/2014	132	2.3	203		0.5		100	400
19/08/2014	135	2.5	184		0.5		50	400
20/11/2014	140	3.2	196		0.5		25	400
19/02/2015	143	2.7	182		0.5		25	400
17/03/2015	142	2.3	233		0.5		0	400
11/08/2015	137	2	183		0.5		0	400

ITP, immune thrombocytopenic purpura.

transitioned to natalizumab. Her platelet count has remained normal.

Case 2

Case 2 was started on prednisolone 1 mg/kg daily and she was given IVIg 1 g/kg 4 days into her admission. She was discharged with improvement in her thrombocytopenia to 29×10^9/L.

Despite being on 75 mg prednisolone daily, her platelet count dropped to 8×10^9/L and she required a second dose of IVIg with an initial response to 97×10^9/L. This was not sustained; she had a platelet count of 38×10^9/L a fortnight later. Given her ongoing need for high-dose steroids, her hydroxychloroquine was increased and azathioprine was instituted 1 month later. Her platelet counts stabilised and she was weaned off all immunosuppression for her thrombocytopenia 7 months later. At this time, she remains in remission 2 years post her initial diagnosis and remains on fingolimod.

Case 3

Case 3 was started on prednisolone 1 mg/kg daily and 4 days later she was given 1 g/kg IVIg. With this, her platelet count stabilised to 200×10^9/L. Unfortunately 1 month into her admission, she developed steroid-induced psychosis necessitating rapid cessation and bridging IVIg. This stabilised her platelet counts for a further month before she required retreatment. She was then started on the steroid-sparing agents, azathioprine 2 mg/kg and hydroxychloroquine 400 mg daily.

Failing to increment her platelets above 10×10^9/L over a month and being a high-risk candidate for splenectomy, she was started on eltrombopag, a thrombopoietin (TPO) mimetic. While on eltrombopag, fingolimod was reinstituted. During this time, her platelet count decreased to 7×10^9/L necessitating a fortnight of prednisolone at doses of 0.5 mg/kg daily and fingolimod was ceased after 2 weeks.

Unfortunately treatment with eltrombopag failed despite several weeks at 75 mg and she was switched to romiplostim, another TPO mimetic, with a good response to 450 mcg.

She had a prolonged 6-month admission due to refractory ITP and deconditioning. Her platelet counts stabilised well on romiplostim. Her azathioprine and hydroxychloroquine have been ceased due to lack of efficacy.

DISCUSSION

To our knowledge, these are the first case studies of ITP associated with fingolimod. None were on any other medications known to cause ITP and routine investigations for infections such as hepatitis B and C, Epstein-Barr virus, cytomegalovirus and *Helicobacter pylori* were negative. A bone marrow biopsy was deferred in cases 1 and 2 and there was no clinical evidence of splenomegaly in all three cases.

It is difficult to distinguish between drug-induced thrombocytopenia (DIT) and ITP given both are largely diagnoses of exclusion and this remains true for case 1 given the timeline of events. Case 2 is unlikely to be DIT given the fingolimod was continued throughout her thrombocytopenia management and immunosuppression cessation, whereas in case 3, the bone marrow biopsy and ongoing requirements for immunosuppression despite fingolimod cessation favour ITP.

There are no reported cases of DIT implicating fingolimod. There is one case report of methylprednisolone-induced thrombocytopenia, whereas the patient was also on fingolimod. This conclusion was based on positive antibody testing to methylprednisolone and on discontinuation of this medication, her platelet count recovered from 1×10^9/L to 178×10^9/L.[7]

Table 4 Case 3 Full blood counts, fingolimod and ITP management

Date	Haemoglobin (g/L)	White Cell Count ($\times 10^9$)	Platelet count ($\times 10^9$)	Prednisolone dose (mg daily)	Fingolimod dose (mg daily)	IVIg (g)	Azathioprine (mg daily)	Hydroxy chloroquine (mg daily)	Eltrombopag (mg daily)	Romiplostim (microg weekly)
01/09/2013	NA	NA	NA		0.5					
12/01/2013	141	3.7	144							
3/04/2014	153	4.5	58							
4/04/2014	NA	NA	23		Ceased					
16/04/2014	146	2.5	4	55						
19/04/2014	134	6.8	9	55		56				
20/04/2014	135	5.4	31	55						
24/04/2014	142	9.2	121	55						
30/04/2014	148	15.1	193	50						
3/05/2014	142	10.2	108	45						
5/05/2014	149	13	115	40						
8/05/2014	142	11.1	160	15						
19/05/2014	124	4.8	5	Ceased		55				
21/05/2014	106	3.1	43							
22/05/2014	114	3.1	80			55				
26/05/2014	114	5.8	288			55				
29/05/2014	106	3.9	4			60	100	400		
1/06/2014	109	4.9	10			60	100	400		
19/06/2014	102	6.1	8	5			100	400		
30/06/2014	112	6.4	27	20			100	400	50	
2/07/2014	123	12.1	45	20			100	400	50	
4/07/2014	119	6.3	45	30	0.5		100	400	50	
5/07/2014	119	6.1	19	Ceased	0.5		100	400	50	
6/07/2014	117	6.1	17		0.5		100	400	50	
10/07/2014	116	6.2	22		0.5		100	400	50	
11/07/2014	121	9	27		0.5		100	400	50	
12/07/2014	120	4.7	7		0.5		100	400	50	
13/07/2014	118	5.3	6	30	Ceased		100	400	50	
19/07/2014	123	5.6	9	20			100	400	50	
20/07/2014	120	6.6	9	30			100	400	75	
23/07/2014	123	6.3	13	30			100	400	75	
2/08/2014	126	7.8	10	15			100	400	75	
7/08/2014	126	7	9	15		66	100	400	75	
20/08/2014	119	4	20	Ceased			100	400	75	
22/08/2014	115	4.5	16				100	400	75	
25/08/2014	114	5.6	29				100	400	Ceased	275
29/08/2014	148	5.6	129				100	400		250
6/10/2014	129	5.4	580				50	400		130
21/10/2014	127	4.9	6			60	50	400		130
23/10/2014	118	3.9	21			60	50	400		250
25/12/2014	101	4.3	30			55	50	400		300
2/03/2015	119	5.7	163				Ceased	Ceased		350
15/04/2015	120	6.3	22							450
29/07/2015	111	6.3	32							450
30/07/2015	120	25.1	153							450

ITP, immune thrombocytopenic purpura.

Certainly fingolimod has significant interactions with platelets. Platelets are significantly activated in patients with MS,[8] and fingolimod phosphorylation, the critical step in converting fingolimod to its active metabolite, occurs in platelets.[9] However, phosphorylation of fingolimod is mostly independent of platelet activation.[9]

Earlier studies showed no effect on platelet function,[10] and none of the 1600 patients exposed to fingolimod in the two largest trials developed thrombocytopenia or significant bleeding.[2 3]

The association between fingolimod and ITP does not fulfil all of Hills criteria of causation.[11] The association lacks strength and consistency given there have been minimal reported cases to date.

However, there was temporal association in all three cases. A dose–response relationship based on our three cases is less clear. Case 1 was on 0.5 mg alternate daily fingolimod and attained complete remission (CR, platelet count $>100\times10^9$/L) in less than a fortnight. In contrast, case 2 continued 0.5 mg daily fingolimod, attained CR in 2 months and required 2 years of immunosuppression. Similarly, case 3 whose fingolimod was ceased

at initial ITP diagnosis attained CR in 2 weeks but required >1 year of treatment. Case 3 suffered five relapses (platelet count $<30\times10^9$/L), one of which was temporally associated with fingolimod reinitiation.

In terms of plausibility, mechanisms linking fingolimod and ITP remain unclear. Paradoxically, fingolimod transiently increased platelets in mouse models via S1pr1 activation on megakaryocytes leading to increased fragmentation of intravascular proplatelets.[12] Thrombocytosis was not found in human trials however.[2 3]

An alternative explanation is autoimmune clustering given MS is 25 times more prevalent in patients with ITP than the general population.[13] It is possible that with lymphocyte sequestration in lymphoid organs, fingolimod allows increased T-cell and B-cell interaction leading to immune dysregulation. In line with this hypothesis, there is a case report of autoimmune haemolytic anaemia felt secondary to fingolimod where cessation was required to abate haemolysis.[14] In addition, there are two cases of fingolimod associated haemophagocytic syndrome,[15 16] a rare disorder of cytokine dysregulation again reflecting a hyperactive immune state.

In conclusion, our cases highlight the possible association between ITP and fingolimod although the mechanism for this remains unclear.

Learning points

- Immune thrombocytopenic purpura (ITP) is a disorder characterised by autoimmune destruction of platelets.
- Medication reconciliation is essential in the management of acute thrombocytopenia.
- There is a possible association between ITP and fingolimod.

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