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Fatigue in immune thrombocytopenia

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Summary

Fatigue is an important aspect of health-related quality of life from the patient perspective and can have significant socio-economic consequences. It is a common feature of chronic illnesses and a significant number of both adults and children with immune thrombocytopenia (ITP) suffer from fatigue. Reliable, validated fatigue scales have been developed for use in ITP. These will facilitate future investigation of its pathogenesis and the effectiveness of intervention. Acute inflammation acts on neural and endocrine systems resulting in 'sickness behaviour', an adaptive response to infection and injury. Inflammation is also thought to cause fatigue in chronic disease and immune dysregulation in ITP appears to have a number of pro-inflammatory components. Clinicians should consider fatigue when assessing the burden of disease. Although effective ITP-directed therapy can improve fatigue, a number of fatigue-directed strategies may also need to be considered.

Keywords: immune thrombocytopenia, fatigue, inflammation, aetiology, quality of life.

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder associated with a reduced platelet count and may present with bruising and bleeding. Primary (idiopathic) ITP is rare, with an incidence of approximately 4–6 per 100 000 per year (Gernsheimer, 2008; Schoonen *et al*, 2009). Bleeding risk rises as the platelet count falls and for patients with a platelet count $<30 \times 10^9$/l, risk of fatal haemorrhage (usually intracranial) has been estimated at 0·016–0·039 cases per patient-year, although factors such as age also affect risk (Cohen *et al*, 2000). However, many have only minor mucosal bleeding or a tendency to bruise easily, one quarter are asymptomatic at presentation and those with mild disease do not usually require treatment. ITP is not purely a bleeding disorder and, paradoxically, an increased rate of venous thrombosis has been observed (Severinsen *et al*, 2011). Patient-reported outcomes help quantify the impact of a disease and its treatments on well being, daily life and physical, psychological and social functioning (Mathias *et al*, 2008). These are typically assessed with a health-related quality of life (HRQoL) questionnaire and HRQoL has been shown to be significantly reduced in patients with ITP compared to controls (McMillan *et al*, 2008; Snyder *et al*, 2008). In one study, HRQoL was similar to patients with diabetes mellitus and worse than those with other chronic diseases including hypertension, arthritis and cancer (McMillan *et al*, 2008).

Fatigue is one of the most common and distressing symptoms for patients with a chronic disease. It is a frequent symptom of autoimmune disorders and affects 80–93% of patients with rheumatoid arthritis (Huyser *et al*, 1998), 50–92% with systemic lupus erythematosis (SLE) (Schmeding & Schneider, 2013) and 68% with primary biliary cirrhosis (Cauch-Dudek *et al*, 1998). The negative impact of fatigue on task completion makes it an important public health issue, and in the United States, workers with fatigue cost employers $136·4 billion annually in lost productive time (Ricci *et al*, 2007). Patients with ITP also complain of fatigue and many feel that they have less energy when the platelet count is low (Cines & Bussel, 2005; Newton *et al*, 2011). We aim to review the evidence that ITP results in fatigue, the reasons why fatigue could develop and future prospects for research and clinical practice.

How do you define and measure fatigue?

Historically, studies of physical illness have rarely addressed fatigue, possibly because it is a subjective complaint that is difficult to define and measure. This lack of a clear and widely accepted definition is illustrated by cancer-related fatigue, for which 24 different definitions have been put forward by experts (Barsevick *et al*, 2010). Fatigue would be typically defined as: extreme and persistent tiredness, weakness or exhaustion – mental, physical or both (Dittner *et al*, 2004). This is usually experienced in the absence of any excessive expenditure of energy as a cause and is often associated with decreased functioning, e.g. difficulty completing tasks.

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In clinical studies, fatigue is usually measured using a self-assessment fatigue scale or questionnaire. This may be uni-dimensional (e.g. the Fatigue Severity Scale), multi-dimensional (e.g. the Visual Analogue Scale for Fatigue) or form part of a broader index of outcome [e.g. the Medical Outcomes Study Short Form-36 (SF-36)]. Fatigue scales [reviewed in detail elsewhere (Dittner *et al*, 2004)] should be reliable, validated and applicable to the patient population being studied. Several disease-specific HRQoL tools that include evaluation of fatigue have been developed for, or validated in ITP patients. For example, the ITP Patient Assessment Questionnaire (ITP-PAQ) has demonstrated acceptable reliability and validity (Mathias *et al*, 2007) and has chiefly been used in clinical trials of romiplostim. In the ITP-PAQ, patients are asked how often in the last 4 weeks did ITP or its treatments cause them to be physically fatigued, on a 5-point scale from 'all the time' to 'never'. In trials of eltrombopag, fatigue was primarily assessed using the fatigue subscale of the Functional Assessment of Chronic Illness Therapy (FACIT-F) questionnaire. FACIT-F was originally designed for use in cancer but has been validated in other chronic diseases and its reliability and validity was also demonstrated in ITP patients, along with the SF-36v2 (Signorovitch *et al*, 2011). The FACIT-F consists of 13 questions related to fatigue, rated on a scale of 0 'not at all' to 4 'very much'.

Do patients with ITP suffer from fatigue?

In a series of focus groups, 14/23 ITP patients identified fatigue as an important issue (Mathias *et al*, 2008). In a qualitative postal survey of patients with primary ITP, 790 patients (696 adults, 94 children) returned a complete survey (45% response rate) (Sarpatwari *et al*, 2010a) and 12·5% 'always' or 'often' missed work or school due to fatigue. A further survey assessed 585 UK and 93 US patients with primary ITP using the Fatigue Impact Scale (FIS) (Newton *et al*, 2011). The FIS is a multidimensional assessment of the impact of fatigue on cognitive, physical and psychosocial function that has been validated in a number of chronic disease states. Significant fatigue (FIS $\geq$ 40) was found in 39% (UK) and 22% (US) of patients, significantly more than the 2·5% expected in normal subjects. A smaller study reported a history of fatigue in 22% (6/27) of children with ITP (Blatt *et al*, 2010). In two controlled trials of romiplostim in ITP (n = 125), the baseline assessment of HRQoL by ITP-PAQ found that of 44 items evaluated, fatigue was among the five worst scores (George *et al*, 2009). In the RAISE study of eltrombopag (n = 197), the mean baseline FACIT-F score was lower in ITP patients than the general US population, suggesting a greater burden of fatigue (Signorovitch *et al*, 2011). Taken together, these studies provide evidence that fatigue occurs in a significant proportion of patients with ITP.

It is less clear whether fatigue is associated with disease severity as measured by the platelet count. In one questionnaire, school or work absence due to fatigue did not significantly correlate to the platelet count (<20, 20–49 or >50 $\times$ 10^9/l) at last follow-up (Sarpatwari *et al*, 2010a) and in an assessment of 236 adult ITP patients with the Chinese (mainland) version of the SF-36, the platelet count (<30, 30–100 > 100 $\times$ 10^9/l) was not a significant predictor of energy/vitality (Zhou *et al*, 2007). In contrast, the study of Newton *et al* (2011) found that 69% of patients in the UK cohort and 50% of patients in the US cohort reported that they had less energy when their platelet count was low. Further analysis revealed that a platelet count <100 $\times$ 10^9/l in patients with bleeding symptoms, and a platelet count <30 $\times$ 10^9/l in patients without bleeding, were independent risk factors for fatigue. Additionally, in a 52 week study of romiplostim *versus* standard of care, overall treatment responders (platelet count $\geq$ 50 $\times$ 10^9/l) had significantly less fatigue (Kuter *et al*, 2012).

Why do patients with ITP become fatigued?

The causes of ITP-associated fatigue are not fully understood. However, there is sufficient understanding of the pathogenesis of fatigue in other chronic diseases to form hypotheses for testing (Fig 1). In some patients, ITP is secondary to a condition such as SLE that is itself associated with fatigue. There may be an associated disorder, such as hypothyroidism, or existing co-morbidities and in one ITP study, the presence of other medical problems was an independent predictor of fatigue (Newton *et al*, 2011). Thrombocytopenia can affect other aspects of HRQoL that may indirectly influence mood and energy levels. For example, in one questionnaire, 23% of children and 9·5% of adults were frustrated by activity restrictions and there was a negative impact on social engagement (Sarpatwari *et al*, 2010a). Sleep and mood disturbance are often associated with fatigue in chronic disease (Nikolaus *et al*, 2013; Schmeding & Schneider, 2013) and daytime sleepiness has been independently associated with ITP-associated fatigue (Newton *et al*, 2011). Pre-morbid psychological symptoms and lack of exercise predict development of chronic fatigue syndrome (CFS) and post-infectious fatigue (Lewis & Wessely, 1992) while early life stress is a risk factor for both inflammation and fatigue in later life (Bower, 2012). Social and behavioural predictors of fatigue in chronic disease include lack of social support (Nikolaus *et al*, 2013; Schmeding & Schneider, 2013), negative interpersonal events (Nikolaus *et al*, 2013), low self-efficacy expectations towards coping (Riemsma *et al*, 1998) or other negative illness beliefs (Joyce *et al*, 1997). Some factors, such as mood, illness belief, social support and ability to work, may be both cause and consequence of fatigue and have a dynamic bi-directional interaction with fatigue (Hewlett *et al*, 2011).

The impact of medical therapy

Medical therapy may influence fatigue, either negatively through toxicity, or positively through disease control. As the

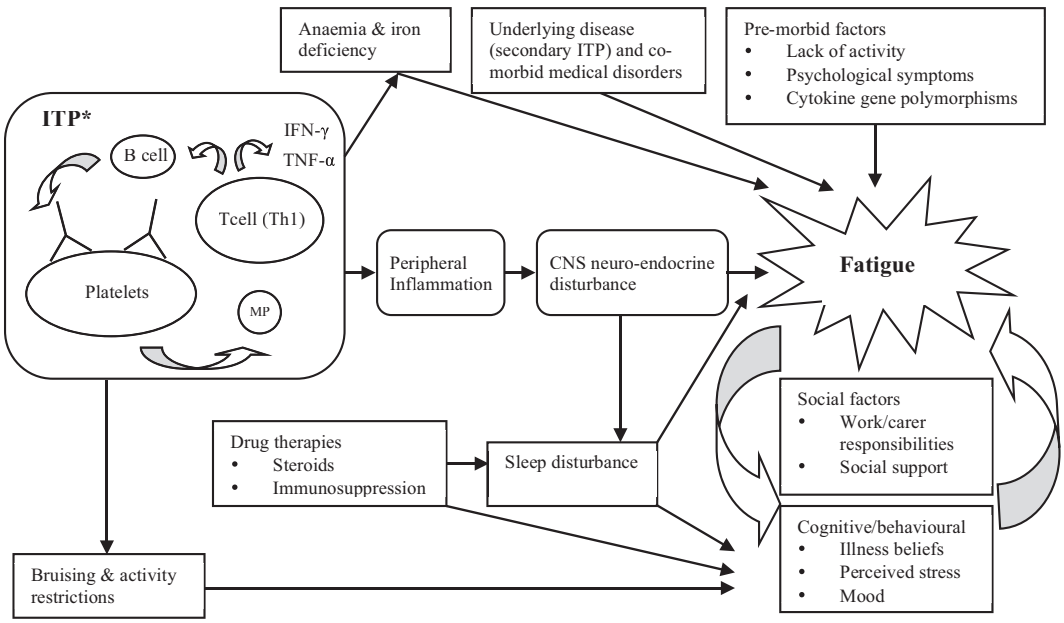

Fig 1. Model of the pathogenesis of ITP-associated fatigue. ITP, immune thrombocytopenia; B cell, autoantibody producing B lymphocytes; T cell Th1, T lymphocytes with a T helper 1 polarization; TNF-α, tumour necrosis factor alpha; IFN-γ, interferon gamma; MP, microparticles; CNS, central nervous system. *T cells can attack platelets directly, secrete pro-inflammatory cytokines and drive formation of autoreactive B cells. This results in antibody- and complement-mediated platelet destruction. Platelet microparticles are prothrombotic and able to activate the proinflammatory complement pathway.

need for therapy is likely to be a surrogate for disease activity, it will be difficult to untangle their relative contribution to fatigue without longitudinal studies. There is little data on the impact of splenectomy on fatigue. In one study, subgroup analysis of a standard of care arm found that HRQoL including fatigue was not significantly different before and after splenectomy but the analysis lacked statistical power (n = 13) (Kuter *et al*, 2012).

Corticosteroids and immunosuppressive therapy

Corticosteroids have multiple side effects that could contribute to fatigue, including sleep disturbance, a range of psychiatric reactions, fluid retention, acne, muscle weakness, proximal myopathy and susceptibility to infection. In a study of 986 adult ITP patients, 25/33 steroid-related symptoms, including fatigue, occurred more frequently in current corticosteroid users than patients who had not received steroids (Berti *et al*, 2008). Fatigue was one of the most frequent and distressing symptoms in both groups. In a further study, fatigue was associated with steroid treatment in univariate but not multivariate analysis (Newton *et al*, 2011).

The side effects of immunosuppressive therapy, such as infection and anaemia, may also lead to fatigue, although the mechanisms of drug induced fatigue are not fully understood (Zlott & Byrne, 2010). Thiopurines, such as azathioprine, have been recognized to cause fatigue in patients with inflammatory bowel disease (Lee *et al*, 2009). In patients with primary refractory ITP receiving ciclosporin, fatigue was reported as a side effect in 2/12 (Emilia *et al*, 2002) and 2/10 (Kappers-Klunne & van't Veer, 2001) cases. In a randomized control trial (RCT) of first line rituximab *versus* rituximab and dexamethasone for primary ITP, fatigue was the most frequently reported adverse event (*c.* 40%) and was not significantly more common with the addition of steroids (Gudbrandsdottir *et al*, 2013). Interestingly, in a placebo-controlled RCT of patients with primary ITP, 22% (7/32) complained of fatigue after receiving rituximab compared with 8% (2/26) receiving placebo, although the difference was not tested for significance (Arnold *et al*, 2012).

Thrombopoietin receptor agents

Thrombopoietin receptor agonists (thrombomimetics) stimulate platelet production and are a relatively targeted therapy. In trials of romiplosim and eltrombopag, fatigue was not reported as an adverse event more frequently than in patients receiving placebo (Cuker, 2010). Thrombomimetics are effective with response rates of approximately 80% (Provan *et al*, 2010). If fatigue is associated with disease severity, effective targeted treatment might be expected to improve fatigue. However despite a reduction in bleeding events and an overall improvement in HRQoL with romiplostim (Kuter *et al*, 2010; Stasi *et al*, 2012) and eltrombopag (Cheng *et al*, 2011; Tarantino *et al*, 2013), neither treatment was able to show a consistent and clinically significant improvement in fatigue. There was no difference in fatigue between eltrombopag and placebo arms when measured by the FACIT-F score,

although a significant improvement in vitality (physical or mental fatigue) in the SF-36v2 was found in the eltrombopag arm compared with baseline and placebo (Cheng *et al*, 2011). When romiplostim was assessed in two phase III trials of splenectomized and non-splenectomized patients after 24 weeks, the ITP-PAQ showed no improvement in fatigue from baseline in patients receiving treatment or placebo (George *et al*, 2009). When non-splenectomized patients were assessed at 52 weeks in an open-label study, the ITP-PAQ fatigue score was significantly improved from baseline after treatment with both standard of care and romiplostim arms. However the change in fatigue for both arms did not meet criteria for a clinically significant improvement. A clinically significant improvement was identified in treatment responders *versus* treatment non-responders and the failure to demonstrate this with romiplostim may therefore reflect dilution of the treatment effect by non-responders (Kuter *et al*, 2012). Alternatively, if ITP-related fatigue is partly driven by immune dysregulation and cytokine pathways, its pathophysiology may not be affected by a targeted thrombomimetic.

Bruising and bleeding

Bruising and bleeding can lead to anaemia and iron deficiency although information is limited on their prevalence in ITP patients. Iron deficiency in pre-menopausal women can cause fatigue, even in the absence of anaemia (Wang *et al*, 2013) and this fatigue is correctable with iron replacement therapy (Krayenbuehl *et al*, 2011). Anaemia may be exacerbated by medical therapy or arise from an underlying cause of ITP. For example, anaemia is found in approximately 50% of patients with SLE (Giannouli *et al*, 2006). An additional consequence of bruising is highlighted by a survey in which 13·5% of women had attempted to conceal bruises and 7% felt people suspected bruising had resulted from physical violence (Sarpatwari *et al*, 2010a). Visible bruising can therefore cause social embarrassment and this was identified by ITP patient focus groups as a limitation on social and leisure activities leading to a reduced HRQoL (Mathias *et al*, 2008). Furthermore, as previously noted, negative social interaction can lead to fatigue. In a postal survey, bruising and bleeding symptoms were significantly associated with fatigue in univariate but not multivariate analysis (Newton *et al*, 2011).

Disease activity

Immune thrombocytopenia is a disorder of immune dysregulation. In other chronic disorders, fatigue appears to be driven by immune activation and pro-inflammatory processes. Although this association awaits investigation in ITP, recent developments in the understanding of its pathophysiology suggest a role for pro-inflammatory cytokines. Cytokines, such as interleukin (IL) 1β (IL1B), IL6 and tumour necrosis factor (TNF) α are normally produced in response to infection or tissue injury. Cytokines can then enter the central nervous system (CNS) through leaky regions of the blood brain barrier, be carried across by transporters, relay cytokine signals by activation of peripheral nerve afferents or recruit activated immune cells which then enter the CNS (Felger & Miller, 2012). This leads to neuroinflammation by stimulating local inflammatory signalling pathways (e.g. nuclear factor kappa B, mitogen-activated protein kinases) and further cytokine production in astrocytes and microglial cells. This in turn alters neurotransmitter metabolism and affects endocrine pathways, for example stimulating corticotrophin releasing hormone (Miller *et al*, 2008) and suppressing thyrotropin releasing hormone (Kamath *et al*, 2009). These central effects promote fever and result in lethargy, anhedonia (loss of ability to experience pleasure), decreased libido, sleep disturbance and anorexia (Adelman & Martin, 2009). This 'sickness behaviour' favours survival by directing energy towards healing and can be reproduced by infusion of IL1 in animals (Dunn, 2006). However, when inflammation persists in chronic disease, these effects are no longer adaptive (Felger & Miller, 2012). The concept of inflammatory sickness behaviour helps explain why the overlapping co-morbidities of depression, sleep disturbance and fatigue are so often seen together in patients with cancer (Miller *et al*, 2008) and chronic disease (Swain, 2000; Nikolaus *et al*, 2013; Schmeding & Schneider, 2013). Inflammatory cytokines are raised in depression (Anderson *et al*, 2014) and CFS (Brenu *et al*, 2011). They are also associated with fatigue in patients with cancer (Schubert *et al*, 2007) and diabetes mellitus (Lasselin *et al*, 2012). In human studies, treatment with interferon (IFN) or IL6 often induces fatigue (Spath-Schwalbe *et al*, 1998) while inhibition of IL6 or TNFα can reduce it (Monk *et al*, 2006; Rohleder *et al*, 2012).

A pro-inflammatory environment in ITP is supported by the observation that thromboembolic events (TE's) can occur in patients despite thrombocytopenia and, in one study, 21% (9/43) of TE's occurred when the platelet count was $<50 \times 10^9$/l (Ruggeri *et al*, 2014). ITP patients who develop thrombosis have been found to have a significantly lower presenting platelet count than those who did not (Ruggeri *et al*, 2014), suggesting thrombosis may be a marker of disease severity. Another study noted a non-significant trend towards a lower presenting platelet count in those who developed TE's (Sarpatwari *et al*, 2010b). Platelets play an important role in thrombosis, inflammation and vascular injury. Proposed mechanisms of thrombosis in ITP include a greater proportion of young activated platelets and greater release of platelet microparticles (Aledort *et al*, 2004; Ruggeri *et al*, 2014). Activated platelets and platelet microparticles have an intrinsic capacity to activate the alternative and classical complement pathways on/near their surface, with measurable increases in soluble inflammatory mediators C3a and C5a (Peerschke *et al*, 2010). This immune-mediated complement activation is found in ITP patients, in whom greater activation is associated with a lower platelet count (Peerschke *et al*,

2010). Additionally, microparticle-associated procoagulant activity has been shown to be higher in ITP patients than healthy controls (Alvarez Roman *et al*, 2014). These observations also support a pro-inflammatory and pro-thrombotic environment in patients with ITP.

The pathogenesis of ITP and the cytokine milieu

The pathogenesis of ITP is likely to be complex and may vary between patients. As well as antibody production by auto-reactive B lymphocytes against platelets and megakaryocytes, there can be platelet lysis by $CD8^+$ cytotoxic lymphocytes (Olsson *et al*, 2003). Although some self-reactive T cells survive as part of the normal immune repertoire, self tolerance mechanisms include control by T regulatory cells (Tregs), while auto-reactive B cells are progressively removed during maturation in the bone marrow (Cooper & Bussel, 2006). In ITP, most studies have found a reduction in circulating Tregs (Semple & Provan, 2012). There is also evidence of an abnormal cytokine environment. A $CD4^+$ T helper cell type 1 (Th1) cell response is characterized by increased IL2, while Th2 cells produce ILs 4, 5, 6, 9, 10 and 13. In patients with ITP, cytokine profiles in plasma and peripheral blood mononuclear cells demonstrate a greater Th1/Th2 profile (Semple *et al*, 1996; Panitsas *et al*, 2004; Wang *et al*, 2005). A Th1 profile is supported by the finding of an increase in the pro-inflammatory IL18, which promotes a Th1 response. In addition, there is a decrease in the anti-inflammatory transforming growth factor beta-1 (TGFβ-1; TGFB1) which would otherwise promote the formation of Tregs and inhibit lymphocyte proliferation and differentiation into Th1 or Th2 phenotypes (Zhao *et al*, 2014).

Further evidence for the significance of inflammatory cytokines in ITP pathogenesis comes from studies showing that certain genetic polymorphisms associated with cytokine production are more likely in ITP patients. For example, carriers of the *IL1RN*2* allele were more common in 122 ITP patients compared with 541 blood donors and this allele was associated with higher IL1 [α (IL1A) and β (IL1B)] levels in both groups (Rocha *et al*, 2010). Gene polymorphisms linked to production of IL2, IL4, IL10, TNFα (TNF), TNFβ (LTA) and the anti-inflammatory IL1 receptor antagonist have also been associated with individuals developing ITP (Rocha *et al*, 2010; Pesmatzoglou *et al*, 2012). This is particularly interesting because variant alleles of pro-inflammatory cytokine genes have been associated with a greater risk of fatigue in cancer patients undergoing various therapies (Bower, 2012).

Some studies have found different plasma cytokine profiles in ITP patients (Del Vecchio *et al*, 2012; Culic *et al*, 2013) and there are a number of potentially confounding variables. The increase in plasma cytokines, such as IL1B following immune challenge is often transient (Wood & Weymann, 2013) and the ability to detect them can deteriorate with suboptimal sample processing, temperature and duration of storage (Schubert *et al*, 2007). An individual's cytokine profile can be further influenced by: age (Ma *et al*, 2008), genetic polymorphisms in genes involved in the pro-inflammatory immune response (Rocha *et al*, 2010), use of therapeutic agents such as steroids (Zhan *et al*, 2014), time of day (Schubert *et al*, 2007), sleep disruption (Schubert *et al*, 2007) and disease activity (Panitsas *et al*, 2004). Absolute individual cytokine levels may be physiologically less important than relative concentrations of antagonizing cytokines (Panitsas *et al*, 2004) and the method of analysing multiple cytokines may need to evolve to understand this, e.g. as components of Th1, Th2 and Th17 responses. For example, in patients with CFS the use of a cytokine co-expression network analysis revealed an established Th2 inflammatory milieu and attenuated Th1 and Th17 immune responses (Broderick *et al*, 2010).

As well as a direct effect of pro-inflammatory cytokines on neurotransmitters, such as serotonin (Anderson *et al*, 2014; Ifuku *et al*, 2014) and dopamine (Felger & Miller, 2012; Bower & Lamkin, 2013), IFNγ (IFNG) and IL6 may also act indirectly by inducing expression of indoleamine 2,3-dioxygenase (IDO). IDO increases breakdown of the serotonin precursor tryptophan via the kynurenine pathway. Several downstream pathway metabolites, such as quinolinic acid and kyurenic acid, also have neuroregulatory activity. Inflammatory IDO induction appears to have an antimicrobial function but it also increases immune tolerance by inducing formation of Tregs and limiting T-cell proliferation (Kwidzinski & Bechmann, 2007). The Th1 cytokine profile seen in ITP patients would be expected to induce IDO and yet, as seen in other autoimmune disorders, there is reduced IDO expression in dendritic cells (Wang *et al*, 2011; Xu *et al*, 2012) resulting in reduced Tregs and impaired self tolerance (Catani *et al*, 2013). The mechanism is unclear and one study found no evidence of impaired IFNγ receptor expression to explain the failure of dendritic cells to up-regulate IDO (Catani *et al*, 2013). A further study found reduced IDO expression in $CD4^+$ and $CD8^+$ T-cells but increased in $CD19^+$ and $CD14^+$ cells (Wang *et al*, 2011). These findings suggest that IDO expression within immune effector cells has an important role in the pathogenesis of ITP. Although not studied in ITP, inflammatory cytokines within the CNS increase IDO expression thereby influencing neuropeptides (Felger & Miller, 2012) and this may be a step in the pathogenesis of fatigue.

Future prospects

A significant proportion of ITP patients suffer from fatigue, but the symptom is less common than in other chronic diseases. With a heterogeneous pathogenesis, ITP therefore presents an opportunity to better understand which aspects of immune dysregulation might lead to fatigue. Studies need to be well powered and longitudinal if they are to determine causality between variables with probable association, such as mood disorder and sleep disturbance. Longitudinal assessment with validated fatigue scales, such as FACIT-F and ITP-PAQ, can also be used to assess the effectiveness of interven-

tions. It would be illuminating to map fatigue symptoms against markers of immune function, such as T and B lymphocyte activity and inflammatory cytokines. The platelet count has limitations as a surrogate marker of ITP disease activity and inflammatory biomarkers could be tested for their association with bleeding score and other aspects of HRQoL as well as fatigue. Potential candidates for further study would include microparticle procoagulant activity, inflammatory gene polymorphisms and cytokines such as IL1β, IL6, IL18, IFNγ, TGFβ1 and neopterin (produced by IFNγ-stimulated monocytes). However extended cytokine analysis may be necessary to fully characterize the profile of an individual's immune dysregulation. Due to the dynamic nature of cytokines, multiple daily blood samples and daily fatigue assessments would be ideal (Schubert *et al*, 2007), with control and documentation of sampling and storage conditions. A limitation of studying plasma is that cytokine levels may not reflect activity in immune effector cells or the CNS. For investigation of the central pathogenesis of fatigue, promising non-invasive imaging techniques include proton magnetic resonance spectroscopic imaging to assess *in-vivo* brain metabolites (Gabbay *et al*, 2010) and positron emission tomography (Capuron *et al*, 2007), however animal models may also be useful in understanding CNS pathways.

In clinical practice, a validated screening tool to identify patients with clinically significant fatigue is needed. Screening could usefully cover other components of HRQoL, such as sleep, mood, family or financial pressures and such general tools exist, for example, The Distress Thermometer Screening Tool, which has been validated for cancer patients (Jacobsen *et al*, 2005). Meanwhile, fatigue should be actively sought, with moderate or severe symptoms prompting more detailed enquiry. Thus far, effective ITP therapy is the best-studied route to improving fatigue but understanding its pathogenesis may present other targets for intervention. For example, potentially treatable factors should be identified, such as sleep disturbance, anaemia or iron deficiency, mood disorder or psychosocial issues, co-morbid disorders and medication side effects. These may require medication but non-pharmacological interventions have been effective in patients with other causes of chronic fatigue. In CFS, illness belief is an important predictor of outcome (Joyce *et al*, 1997) and interventions such as education, cognitive behavioural therapy (CBT) and exercise have GRADE 1A evidence for their effectiveness. The importance of stress reduction and sleep are also emphasized with a focus on self management strategies (Clauw, 2014). In patients with cancer-associated fatigue, yoga and CBT were both shown to reduce inflammatory markers and fatigue symptoms (Bower & Lamkin, 2013). Other non-pharmacological approaches to cancer-associated fatigue include physical activity, complementary therapies (e.g. relaxation, massage, acupuncture), energy conservation (finding a balanced routine of activity and rest), sleep therapies (e.g. sleep hygiene through comfortable sleep surroundings and avoiding caffeine or exercise before sleep) and psychosocial therapies (counselling, spiritual care and distraction, e.g. reading, walking or gardening) (Koornstra *et al*, 2014).

Although no fatigue-directed pharmacological therapy is yet in use, there are a number of potential candidates. In a meta-analysis of 8 randomized controlled trials of adjunctive melatonin 20 mg once daily during chemotherapy or radiotherapy for solid organ cancer, it was shown to significantly reduce fatigue ($P < 0{\cdot}00001$) (Wang *et al*, 2012). In patients with CFS, a cross-over study ($n = 63$) found agomelatine, a melatonin receptor agonist and serotonin-2C receptor antagonist that increases pre-frontal dopaminergic and noradrenergic tone, significantly reduced fatigue (Pardini *et al*, 2014). A small randomized placebo-controlled study found a significant reduction in cancer-associated fatigue and sleep disturbance in patients receiving thyrotropin releasing hormone (Kamath *et al*, 2009). Dopaminergic therapies, such as methylphenidate, amantadine and modafinil, have also been used to combat fatigue but with mixed results (Peuckmann *et al*, 2010; Sheng *et al*, 2013).

Conclusion

Fatigue is an important morbidity from the patient perspective. The presence of fatigue has been established in a significant proportion of patients with ITP. The development of validated, reproducible, disease-specific tools for accessing HRQoL and fatigue has now paved the way for further enquiry into its pathogenesis. Studies of fatigue in chronic disease have found an association between fatigue and symptoms, such as mood and sleep disturbance, and these may be linked through inflammatory processes. The reasons for fatigue are likely to be multiple, vary between individuals and vary for an individual during the course of their illness and treatment. Longitudinal studies are needed to explore the factors contributing to ITP-related fatigue.

Clinicians should assess fatigue symptoms and other aspects of HRQoL alongside lifestyle, bleeding symptoms and the platelet count when considering when to intervene with ITP-directed therapy. The effectiveness of non-pharmacological interventions for fatigue have not been studied in ITP patients but are effective in other chronic disorders, have few adverse effects and may be underutilized.

Author contributions

Both authors contributed to the design and writing of the manuscript.

Conflict of interest

QAH has received travel expenses for educational meetings and chaired meetings for Amgen. ACN has been on an Advisory Board for Amgen, Lectured for Amgen, GSK and Roche and has received research support from Amgen, GSK, Octapharma and Rigel.

References

Adelman, J.S. & Martin, L.B. (2009) Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. *Integrative and Comparative Biology*, **49**, 202–214.

Aledort, L.M., Hayward, C.P., Chen, M.G., Nichol, J.L. & Bussel, J. (2004) Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *American Journal of Hematology*, **76**, 205–213.

Alvarez Roman, M.T., Fernandez Bello, I., Arias-Salgado, E.G., Rivas Pollmar, M.I., Jimenez Yuste, V., Martin Salces, M. & Butta, N.V. (2014) Effects of thrombopoietin receptor agonists on procoagulant state in patients with immune thrombocytopenia. *Thrombosis and Haemostasis*, **112**, 65–72.

Anderson, G., Berk, M. & Maes, M. (2014) Biological phenotypes underpin the physio-somatic symptoms of somatization, depression, and chronic fatigue syndrome. *Acta Psychiatrica Scandinavica*, **129**, 83–97.

Arnold, D.M., Heddle, N.M., Carruthers, J., Cook, D.J., Crowther, M.A., Meyer, R.M., Liu, Y., Cook, R.J., McLeod, A., MacEachern, J.A., Mangel, J., Anderson, D., Vickars, L., Tinmouth, A., Schuh, A.C. & Kelton, J.G. (2012) A pilot randomized trial of adjuvant rituximab or placebo for nonsplenectomized patients with immune thrombocytopenia. *Blood*, **119**, 1356–1362.

Barsevick, A.M., Cleeland, C.S., Manning, D.C., O'Mara, A.M., Reeve, B.B., Scott, J.A. & Sloan, J.A. (2010) ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *Journal of Pain and Symptom Management*, **39**, 1086–1099.

Berti, D., Moons, P., Dobbels, F., Deuson, R., Janssens, A. & De, G.S. (2008) Impact of corticosteroid-related symptoms in patients with immune thrombocytopenic purpura: results of a survey of 985 patients. *Clinical Therapeutics*, **30**, 1540–1552.

Blatt, J., Weston, B. & Gold, S. (2010) Fatigue as marker of thrombocytopenia in childhood idiopathic thrombocytopenic purpura. *Pediatric Hematology and Oncology*, **27**, 65–67.

Bower, J.E. (2012) Fatigue, brain, behavior, and immunity: summary of the 2012 Named Series on fatigue. *Brain, Behavior, and Immunity*, **26**, 1220–1223.

Bower, J.E. & Lamkin, D.M. (2013) Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. *Brain, Behavior, and Immunity*, **30**, S48–S57.

Brenu, E.W., Van Driel, M.L., Staines, D.R., Ashton, K.J., Ramos, S.B., Keane, J., Klimas, N.G. & Marshall-Gradisnik, S.M. (2011) Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Journal of Translational Medicine*, **9**, 81.

Broderick, G., Fuite, J., Kreitz, A., Vernon, S.D., Klimas, N. & Fletcher, M.A. (2010) A formal analysis of cytokine networks in chronic fatigue syndrome. *Brain, Behavior, and Immunity*, **24**, 1209–1217.

Capuron, L., Pagnoni, G., Demetrashvili, M.F., Lawson, D.H., Fornwalt, F.B., Woolwine, B., Berns, G.S., Nemeroff, C.B. & Miller, A.H. (2007) Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. *Neuropsychopharmacology*, **32**, 2384–2392.

Catani, L., Sollazzo, D., Trabanelli, S., Curti, A., Evangelisti, C., Polverelli, N., Palandri, F., Baccarani, M., Vianelli, N. & Lemoli, R.M. (2013) Decreased expression of indoleamine 2,3-dioxygenase 1 in dendritic cells contributes to impaired regulatory T cell development in immune thrombocytopenia. *Annals of Hematology*, **92**, 67–78.

Cauch-Dudek, K., Abbey, S., Stewart, D.E. & Heathcote, E.J. (1998) Fatigue in primary biliary cirrhosis. *Gut*, **43**, 705–710.

Cheng, G., Saleh, M.N., Marcher, C., Vasey, S., Mayer, B., Aivado, M., Arning, M., Stone, N.L. & Bussel, J.B. (2011) Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet*, **377**, 393–402.

Cines, D.B. & Bussel, J.B. (2005) How I treat idiopathic thrombocytopenic purpura (ITP). *Blood*, **106**, 2244–2251.

Clauw, D.J. (2014) Fibromyalgia: a clinical review. *JAMA*, **311**, 1547–1555.

Cohen, Y.C., Djulbegovic, B., Shamai-Lubovitz, O. & Mozes, B. (2000) The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Archives of Internal Medicine*, **160**, 1630–1638.

Cooper, N. & Bussel, J. (2006) The pathogenesis of immune thrombocytopenic purpura. *British Journal of Haematology*, **133**, 364–374.

Cuker, A. (2010) Toxicities of the thrombopoietic growth factors. *Seminars in Hematology*, **47**, 289–298.

Culic, S., Salamunic, I., Konjevoda, P., Dajak, S. & Pavelic, J. (2013) Immune thrombocytopenia: serum cytokine levels in children and adults. *Medical Science Monitor*, **19**, 797–801.

Del Vecchio, G.C., Giordano, P., Tesse, R., Piacente, L., Altomare, M. & De, M.D. (2012) Clinical significance of serum cytokine levels and thrombopoietic markers in childhood idiopathic thrombocytopenic purpura. *Blood Transfusion*, **10**, 194–199.

Dittner, A.J., Wessely, S.C. & Brown, R.G. (2004) The assessment of fatigue: a practical guide for clinicians and researchers. *Journal of Psychosomatic Research*, **56**, 157–170.

Dunn, A.J. (2006) Effects of cytokines and infections on brain neurochemistry. *Clinical Neuroscience Research*, **6**, 52–68.

Emilia, G., Morselli, M., Luppi, M., Longo, G., Marasca, R., Gandini, G., Ferrara, L., D'Apollo, N., Potenza, L., Bertesi, M. & Torelli, G. (2002) Long-term salvage therapy with cyclosporin A in refractory idiopathic thrombocytopenic purpura. *Blood*, **99**, 1482–1485.

Felger, J.C. & Miller, A.H. (2012) Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Frontiers in Neuroendocrinology*, **33**, 315–327.

Gabbay, V., Liebes, L., Katz, Y., Liu, S., Mendoza, S., Babb, J.S., Klein, R.G. & Gonen, O. (2010) The kynurenine pathway in adolescent depression: preliminary findings from a proton MR spectroscopy study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **34**, 37–44.

George, J.N., Mathias, S.D., Go, R.S., Guo, M., Henry, D.H., Lyons, R., Redner, R.L., Rice, L. & Schipperus, M.R. (2009) Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials. *British Journal of Haematology*, **144**, 409–415.

Gernsheimer, T. (2008) Epidemiology and pathophysiology of immune thrombocytopenic purpura. *European Journal of Haematology. Supplementum*, **69**, 3–8.

Giannouli, S., Voulgarelis, M., Ziakas, P.D. & Tzioufas, A.G. (2006) Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment. *Annals of the Rheumatic Diseases*, **65**, 144–148.

Gudbrandsdottir, S., Birgens, H.S., Frederiksen, H., Jensen, B.A., Jensen, M.K., Kjeldsen, L., Klausen, T.W., Larsen, H., Mourits-Andersen, H.T., Nielsen, C.H., Nielsen, O.J., Plesner, T., Pulczynski, S., Rasmussen, I.H., Ronnov-Jessen, D. & Hasselbalch, H.C. (2013) Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. *Blood*, **121**, 1976–1981.

Hewlett, S., Chalder, T., Choy, E., Cramp, F., Davis, B., Dures, E., Nicholls, C. & Kirwan, J. (2011) Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology (Oxford)*, **50**, 1004–1006.

Huyser, B.A., Parker, J.C., Thoreson, R., Smarr, K.L., Johnson, J.C. & Hoffman, R. (1998) Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis and Rheumatism*, **41**, 2230–2237.

Ifuku, M., Hossain, S.M., Noda, M. & Katafuchi, T. (2014) Induction of interleukin-1beta by activated microglia is a prerequisite for immunologically induced fatigue. *European Journal of Neuroscience*, **40**, 3253–3263.

Jacobsen, P.B., Donovan, K.A., Trask, P.C., Fleishman, S.B., Zabora, J., Baker, F. & Holland, J.C. (2005) Screening for psychologic distress in ambulatory cancer patients. *Cancer*, **103**, 1494–1502.

Joyce, J., Hotopf, M. & Wessely, S. (1997) The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. *QJM*, **90**, 223–233.

Kamath, J., Yarbrough, G.G., Prange, Jr, A.J. & Winokur, A. (2009) The thyrotropin-releasing hormone (TRH)-immune system homeostatic

hypothesis. *Pharmacology & Therapeutics*, **121**, 20–28.

Kappers-Klunne, M.C. & van't Veer, M.B. (2001) Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. *British Journal of Haematology*, **114**, 121–125.

Koornstra, R.H., Peters, M., Donofrio, S., van den Borne, B. & de Jong, F.A. (2014) Management of fatigue in patients with cancer – a practical overview. *Cancer Treatment Reviews*, **40**, 791–799.

Krayenbuehl, P.A., Battegay, E., Breymann, C., Furrer, J. & Schulthess, G. (2011) Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. *Blood*, **118**, 3222–3227.

Kuter, D.J., Rummel, M., Boccia, R., Macik, B.G., Pabinger, I., Selleslag, D., Rodeghiero, F., Chong, B.H., Wang, X. & Berger, D.P. (2010) Romiplostim or standard of care in patients with immune thrombocytopenia. *New England Journal of Medicine*, **363**, 1889–1899.

Kuter, D.J., Mathias, S.D., Rummel, M., Mandanas, R., Giagounidis, A.A., Wang, X. & Deuson, R.R. (2012) Health-related quality of life in non-splenectomized immune thrombocytopenia patients receiving romiplostim or medical standard of care. *American Journal of Hematology*, **87**, 558–561.

Kwidzinski, E. & Bechmann, I. (2007) IDO expression in the brain: a double-edged sword. *Journal of Molecular Medicine (Berlin)*, **85**, 1351–1359.

Lasselin, J., Laye, S., Dexpert, S., Aubert, A., Gonzalez, C., Gin, H. & Capuron, L. (2012) Fatigue symptoms relate to systemic inflammation in patients with type 2 diabetes. *Brain, Behavior, and Immunity*, **26**, 1211–1219.

Lee, T.W., Iser, J.H., Sparrow, M.P., Newnham, E.D., Headon, B.J. & Gibson, P.R. (2009) Thiopurines, a previously unrecognised cause for fatigue in patients with inflammatory bowel disease. *Journal of Crohn's and Colitis*, **3**, 196–199.

Lewis, G. & Wessely, S. (1992) The epidemiology of fatigue: more questions than answers. *Journal of Epidemiology and Community Health*, **46**, 92–97.

Ma, D., Zhu, X., Zhao, P., Zhao, C., Li, X., Zhu, Y., Li, L., Sun, J., Peng, J., Ji, C. & Hou, M. (2008) Profile of Th17 cytokines (IL-17, TGF-beta, IL-6) and Th1 cytokine (IFN-gamma) in patients with immune thrombocytopenic purpura. *Annals of Hematology*, **87**, 899–904.

Mathias, S.D., Bussel, J.B., George, J.N., McMillan, R., Okano, G.J. & Nichol, J.L. (2007) A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. *Health and Quality of Life Outcomes*, **5**, 11.

Mathias, S.D., Gao, S.K., Miller, K.L., Cella, D., Snyder, C., Turner, R., Wu, A., Bussel, J.B., George, J.N., McMillan, R., Wysocki, D.K. & Nichol, J.L. (2008) Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. *Health and Quality of Life Outcomes*, **6**, 13.

McMillan, R., Bussel, J.B., George, J.N., Lalla, D. & Nichol, J.L. (2008) Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. *American Journal of Hematology*, **83**, 150–154.

Miller, A.H., Ancoli-Israel, S., Bower, J.E., Capuron, L. & Irwin, M.R. (2008) Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *Journal of Clinical Oncology*, **26**, 971–982.

Monk, J.P., Phillips, G., Waite, R., Kuhn, J., Schaaf, L.J., Otterson, G.A., Guttridge, D., Rhoades, C., Shah, M., Criswell, T., Caligiuri, M.A. & Villalona-Calero, M.A. (2006) Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *Journal of Clinical Oncology*, **24**, 1852–1859.

Newton, J.L., Reese, J.A., Watson, S.I., Vesely, S.K., Bolton-Maggs, P.H., George, J.N. & Terrell, D.R. (2011) Fatigue in adult patients with primary immune thrombocytopenia. *European Journal of Haematology*, **86**, 420–429.

Nikolaus, S., Bode, C., Taal, E. & van de Laar, M.A. (2013) Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care & Research*, **65**, 1128–1146.

Olsson, B., Andersson, P.O., Jernas, M., Jacobsson, S., Carlsson, B., Carlsson, L.M. & Wadenvik, H. (2003) T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nature Medicine*, **9**, 1123–1124.

Panitsas, F.P., Theodoropoulou, M., Kouraklis, A., Karakantza, M., Theodorou, G.L., Zoumbos, N.C., Maniatis, A. & Mouzaki, A. (2004) Adult chronic idiopathic thrombocytopenic purpura (ITP) is the manifestation of a type-1 polarized immune response. *Blood*, **103**, 2645–2647.

Pardini, M., Cordano, C., Benassi, F., Mattei, C., Sassos, D., Guida, S., Serrati, C., Primavera, A., Amore, M., Cocito, L. & Emberti, G.L. (2014) Agomelatine but not melatonin improves fatigue perception: a longitudinal proof-of-concept study. *European Neuropsychopharmacology*, **24**, 939–944.

Peerschke, E.I., Andemariam, B., Yin, W. & Bussel, J.B. (2010) Complement activation on platelets correlates with a decrease in circulating immature platelets in patients with immune thrombocytopenic purpura. *British Journal of Haematology*, **148**, 638–645.

Pesmatzoglou, M., Lourou, M., Goulielmos, G.N. & Stiakaki, E. (2012) DNA methyltransferase 3B gene promoter and interleukin-1 receptor antagonist polymorphisms in childhood immune thrombocytopenia. *Clinical & Developmental Immunology*, **2012**, 352059.

Peuckmann-Post, V., Elsner, F., Krumm, N., Trottenberg, P. & Radbruch, L. (2010) Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Systematic Review*, Issue 11, CD006788.

Provan, D., Stasi, R., Newland, A.C., Blanchette, V.S., Bolton-Maggs, P., Bussel, J.B., Chong, B.H., Cines, D.B., Gernsheimer, T.B., Godeau, B., Grainger, J., Greer, I., Hunt, B.J., Imbach, P.A., Lyons, G., McMillan, R., Rodeghiero, F., Sanz, M.A., Tarantino, M., Watson, S., Young, J. & Kuter, D.J. (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*, **115**, 168–186.

Ricci, J.A., Chee, E., Lorandeau, A.L. & Berger, J. (2007) Fatigue in the U.S. workforce: prevalence and implications for lost productive work time. *Journal of Occupational and Environmental Medicine*, **49**, 1–10.

Riemsma, R.P., Rasker, J.J., Taal, E., Griep, E.N., Wouters, J.M. & Wiegman, O. (1998) Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. *British Journal of Rheumatology*, **37**, 1042–1046.

Rocha, A.M., De, S.C., Rocha, G.A., De Melo, F.F., Saraiva, I.S., Clementino, N.C., Marino, M.C. & Queiroz, D.M. (2010) IL1RN VNTR and IL2-330 polymorphic genes are independently associated with chronic immune thrombocytopenia. *British Journal of Haematology*, **150**, 679–684.

Rohleder, N., Aringer, M. & Boentert, M. (2012) Role of interleukin-6 in stress, sleep, and fatigue. *Annals of the New York Academy of Sciences*, **1261**, 88–96.

Ruggeri, M., Tosetto, A., Palandri, F., Polverelli, N., Mazzucconi, M.G., Santoro, C., Gaidano, G., Lunghi, M., Zaja, F., De Stefano, V., Sartori, R., Fazi, P. & Rodeghiero, F. (2014) Thrombotic risk in patients with primary immune thrombocytopenia is only mildly increased and explained by personal and treatment-related risk factors. *Journal of Thrombosis and Haemostasis*, **12**, 1266–1273.

Sarpatwari, A., Watson, S., Erqou, S., Anderson, H., Grainger, J., Higgins, J.P. & Newland, A.C. (2010a) Health-related lifestyle in adults and children with primary immune thrombocytopenia (ITP). *British Journal of Haematology*, **151**, 189–191.

Sarpatwari, A., Bennett, D., Logie, J.W., Shukla, A., Beach, K.J., Newland, A.C., Sanderson, S. & Provan, D. (2010b) Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. *Haematologica*, **95**, 1167–1175.

Schmeding, A. & Schneider, M. (2013) Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Practice & Research. Clinical Rheumatology*, **27**, 363–375.

Schoonen, W.M., Kucera, G., Coalson, J., Li, L., Rutstein, M., Mowat, F., Fryzek, J. & Kaye, J.A. (2009) Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *British Journal of Haematology*, **145**, 235–244.

Schubert, C., Hong, S., Natarajan, L., Mills, P.J. & Dimsdale, J.E. (2007) The association between

fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain, Behavior, and Immunity*, **21**, 413–427.

Semple, J.W. & Provan, D. (2012) The immunopathogenesis of immune thrombocytopenia: T cells still take center-stage. *Current Opinion in Hematology*, **19**, 357–362.

Semple, J.W., Milev, Y., Cosgrave, D., Mody, M., Hornstein, A., Blanchette, V. & Freedman, J. (1996) Differences in serum cytokine levels in acute and chronic autoimmune thrombocytopenic purpura: relationship to platelet phenotype and antiplatelet T-cell reactivity. *Blood*, **87**, 4245–4254.

Severinsen, M.T., Engebjerg, M.C., Farkas, D.K., Jensen, A.O., Norgaard, M., Zhao, S. & Sorensen, H.T. (2011) Risk of venous thromboembolism in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. *British Journal of Haematology*, **152**, 360–362.

Sheng, P., Hou, L., Wang, X., Wang, X., Huang, C., Yu, M., Han, X. & Dong, Y. (2013) Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. *PLoS ONE*, **8**, e81802.

Signorovitch, J., Brainsky, A. & Grotzinger, K.M. (2011) Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. *Quality of Life Research*, **20**, 1737–1744.

Snyder, C.F., Mathias, S.D., Cella, D., Isitt, J.J., Wu, A.W. & Young, J. (2008) Health-related quality of life of immune thrombocytopenic purpura patients: results from a web-based survey. *Current Medical Research and Opinion*, **24**, 2767–2776.

Spath-Schwalbe, E., Hansen, K., Schmidt, F., Schrezenmeier, H., Marshall, L., Burger, K., Fehm, H.L. & Born, J. (1998) Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *Journal of Clinical Endocrinology and Metabolism*, **83**, 1573–1579.

Stasi, R., Murali, M., Michel, M., Viallard, J.F., Giagounidis, A., Janssens, A., Legg, J., Deuson, R. & Danese, M.D. (2012) Evaluation of bleeding-related episodes in patients with immune thrombocytopenia (ITP) receiving romiplostim or medical standard of care. *International Journal of Hematology*, **96**, 26–33.

Swain, M.G. (2000) Fatigue in chronic disease. *Clinical Science (London, England: 1979)*, **99**, 1–8.

Tarantino, M.D., Fogarty, P., Mayer, B., Vasey, S.Y. & Brainsky, A. (2013) Efficacy of eltrombopag in management of bleeding symptoms associated with chronic immune thrombocytopenia. *Blood Coagulation & Fibrinolysis*, **24**, 284–296.

Wang, T., Zhao, H., Ren, H., Guo, J., Xu, M., Yang, R. & Han, Z.C. (2005) Type 1 and type 2 T-cell profiles in idiopathic thrombocytopenic purpura. *Haematologica*, **90**, 914–923.

Wang, C.Y., Shi, Y., Min, Y.N., Zhu, X.J., Guo, C.S., Peng, J., Dong, X.Y., Qin, P., Sun, J.Z. & Hou, M. (2011) Decreased IDO activity and increased TTS expression break immune tolerance in patients with immune thrombocytopenia. *Journal of Clinical Immunology*, **31**, 643–649.

Wang, Y.M., Jin, B.Z., Ai, F., Duan, C.H., Lu, Y.Z., Dong, T.F. & Fu, Q.L. (2012) The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials. *Cancer Chemotherapy and Pharmacology*, **69**, 1213–1220.

Wang, W., Bourgeois, T., Klima, J., Berlan, E.D., Fischer, A.N. & O'Brien, S.H. (2013) Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. *Haemophilia*, **19**, 225–230.

Wood, L.J. & Weymann, K. (2013) Inflammation and neural signaling: etiologic mechanisms of the cancer treatment-related symptom cluster. *Current Opinion in Supportive and Palliative Care*, **7**, 54–59.

Xu, S.Q., Wang, C.Y., Zhu, X.J., Dong, X.Y., Shi, Y., Peng, J., Qin, P., Sun, J.Z., Guo, C., Ni, H. & Hou, M. (2012) Decreased indoleamine 2,3-dioxygenase expression in dendritic cells and role of indoleamine 2,3-dioxygenase-expressing dendritic cells in immune thrombocytopenia. *Annals of Hematology*, **91**, 1623–1631.

Zhan, Y., Zou, S., Hua, F., Li, F., Ji, L., Wang, W., Ye, Y., Sun, L., Chen, H. & Cheng, Y. (2014) High-dose dexamethasone modulates serum cytokine profile in patients with primary immune thrombocytopenia. *Immunology Letters*, **160**, 33–38.

Zhao, H., Li, H., Du, W., Zhang, D., Ge, J., Xue, F., Zhou, Z. & Yang, R. (2014) Reduced MIR130A is involved in primary immune thrombocytopenia via targeting TGFB1 and IL18. *British Journal of Haematology*, **166**, 767–773.

Zhou, Z., Yang, L., Chen, Z., Chen, X., Guo, Y., Wang, X., Dong, X., Wang, T., Zhang, L., Qiu, Z. & Yang, R. (2007) Health-related quality of life measured by the Short Form 36 in immune thrombocytopenic purpura: a cross-sectional survey in China. *European Journal of Haematology*, **78**, 518–523.

Zlott, D.A. & Byrne, M. (2010) Mechanisms by which pharmacologic agents may contribute to fatigue. *PM & R: The Journal of Injury, Function, and Rehabilitation*, **2**, 451–455.