Requirement to treat

Citation	LOE	Study design	Patient numbers	Summary
Vianelli et al. *Haematologica* 2001;86:504–509	IIb	Retrospective analysis of a series of 310 patients with chronic ITP to determine the risk of major bleeding in elderly patients and in patients with bleeding at diagnosis	310	Symptomatic patients more likely to have bleeding during follow-up. Age >60 years not associated with any significant differences in incidence of bleeding at diagnosis or follow-up. Prospective studies required to evaluate whether it may be reasonable to treat only symptomatic patients, independently of age
Zimmer et al. *Clin Lab Haematol* 2004;26:137–142	IIb	Retrospective review of a cohort of consecutive patients with ITP to analyse the therapies used, their response rates, prognostic indicators of response and outcome	201	Patients with moderate thrombocytopenia do not require treatment (n=201)
Andersson et al. *Blood* 2006;108:abs 3959	III	Case study of two elderly ITP patients with minor bleeding	2	Platelet counts normalised spontaneously within 3 months, raising the possibility that select adult ITP patients may not require treatment
Portielje et al. *Blood* 2001;97:2549–2554	IIa	A follow-up study in a cohort of consecutive patients with ITP treated according to a well-defined algorithm, to determine long term outcomes relative to the response 2 years after diagnosis	152	Most patients attained a partial or CR with infrequent hospital admissions and no excess mortality, which supports clinical practice refraining from further treatment
Henderson et al. *J Oral Maxillofac Surg* 2001;59:421–427	III	A review of platelet physiology and platelet disorders that affect the management of thrombocytopathic oral and maxillofacial surgery patients	N/A	Careful pre-operative evaluation needed to help surgeons treat thrombocytopathic oral and maxillofacial patients and help prevent potentially catastrophic intraoperative or post-operative bleeding
Samama et al. *Minerva Anestesiol* 2006;72:447–452	IV	A review of the literature on perioperative platelet transfusions	N/A	Recommendations based on professional consensus were formulated to define threshold platelet counts for perioperative transfusions

Prednisone

Citation	LOE	Study design	Patient numbers	Summary
Gernsheimer et al. *Blood* 2006;108:abs 3990	IIb	Retrospective chart review to characterise the standard of care in a group of patients with ITP	135	Primary measure: initial ITP therapy was prednisone in 70% (n=60) of patients and prednisone plus IVIg in 22% (n=19); remaining 8% (n=7) received other initial therapy Primary outcome: splenectomy performed in 20% patients receiving prednisone monotherapy and 32% receiving prednisone plus IVIg after an average of 149 and 244 days, respectively
Pamuk et al. *Ann Haematol* 2002;81:436–440	IIb	Retrospective study to evaluate the clinical features and effects of various treatment modalities on the clinical course, in patients diagnosed with ITP at a centre between 1984 and 2000	321	Primary measure: CR was defined as any platelet count >100,000/mm^3 lasting for 3 months or longer without treatment Primary outcome: CR achieved in 51.9% of patients given steroids as initial therapy. During median follow-up of 33 months, relapse occurred in 58.2% of these patients; after a median follow-up of 11 months the rest were still in remission. The 10-year disease-free survival in patients who used steroids was 13%. Steroids induced nearly similar rates of CR both as first- and second-line therapies
Feudjo-Tepie et al. ASH 2007:abs 3922	IIb	Retrospective matched cohort study in which each ITP patient was matched to 5 non-ITP control patients to quantify the underlying risk of cataracts among ITP patients compared with non-ITP patients.	745	Primary measure: cataract incidence among ITP and non-ITP steroid users Primary outcome: ITP users of oral steroids had a cataract incidence rate of 14.0 per 1000 person-years (PY) (95% CI: 8.7–21.4) and non-steroid users, a rate of 6.1 per 1000 PY (95% CI: 2.7–11.4). In the non-ITP population, these figures were 16.9 per 1000 PY (95% CI: 11.9–23.3) and 9.2 per 1000 PY (95% CI: 7.6–11.0), respectively. No evidence of an increase in cataracts between ITP vs non-ITP matched cohort
Kaya et al. *Med Princ Pract* 2007;16:100–106	IIb	Retrospective evaluation of the clinical features and effects of various treatment modalities on the clinical course in patients diagnosed with ITP	168	Primary measure: remission following treatment Primary outcome: complete remission achieved in 56% of patients. 61 patients who were followed up regularly received second-line therapies. Complete remission was achieved in 45.8% of the patients who received steroids as second-line therapy. 10-

				year DFS was 15% for those who underwent steroid first-line therapy
Aledort et al. *Am J Hematol* 2004;76:205–213	III	Prospective, exploratory study characterising patients with ITP including diagnosis, serological markers, and the relationship between platelet markers, endogenous thrombopoietin, and circulating antithrombopoietin antibodies	205	Primary measure: demographic and comorbid clinical factors, use of treatments, serological markers of autoimmunity, possible relationships between platelet counts, concentrations of endogenous thrombopoietin (eTPO), presence of circulating antiTPO antibodies Primary outcome: no significant inverse correlation occurred between circulating concentrations of eTPO and platelet counts in patients with ITP. Most common treatment of ITP patients: prednisolone (84%; n=618)
Aledort et al. *Blood* 2006;108:abs 3295	IIb	Retrospective claims analysis using the PharMetrics Integrated Medical and Pharmaceutical Database to compare risks of disease complications in ITP patients and age- and gender-matched non-ITP controls	21,196	Primary measure: incidence of disease complications in ITP patients Primary outcome: ITP patients at greater risk of long-term steroid complications than non-ITP age- and gender-matched controls. Dose-response relationship with event risk was evident
Houwerzjil et al. ASH 2007:abs 1325	IIb	The predictive value of clinical and platelet kinetic parameter for treatment outcome in ITP was investigated	75	Primary measure: clinical and platelet kinetic parameters between responders and non-responders to prednisone therapy Primary outcome: ITP patients with suppressed platelet production rate had a significantly higher durable CR/partial response (PR) rate to prednisone therapy; durable CR/PR in 64% patients with decreased PPR vs 34% patients with normal or increased PPR

High-dose dexamethasone

Citation	LOE	Study design	Patient numbers	Summary
Mazzucconi et al. *Blood* 2007;109:1401–1407	IIa	2 prospective pilot studies (monocentric and multicentric) concerning the use of repeated pulses of HD-DXM in untreated ITP patients	37 and 95	Primary measure: response rate, relapse-free survival, long-term response following repeated pulses of HD-DXM in untreated ITP patients Primary outcome: response rate 89.2%, relapse-free survival 90% at 15 months, long-term responses, lasting for median time of 26 months (range 6–77 months), were 25 of 37 (67.6%). HD-

				DXM may be effective as first-line therapy, study included adults and children
Cheng et al. *N Eng J Med* 2003;349:831–836	IIa	Cohort study to assess the effectiveness of HD-DXM as initial treatment in a series of consecutive adults with ITP	157	Primary measure: response and sustained response following treatment with HD-DXM in adults with ITP Primary outcome: 106 patients responded, 50% had a sustained response; the other 50% had a relapse within 6 months, most of them (94%) within the first 3 months. HD-DXM may be effective as first-line therapy
Stasi et al. *Blood Cells Mols Dis* 2000;26:582–586	IIa	Cohort study in chronic ITP patients to investigate the effectiveness and side effects of HD DXM in patients with chronic ITP	32	Primary measure: Response rate in patients with chronic ITP following 6-monthly courses of IV HD-DXM at the dose of 40 mg/day for 4 consecutive days Primary outcome: 13 patients had a PR or CR, mostly transient. 3 patients failed to respond and clinically required other treatment. HD-DXM limited effect in patients with refractory ITP
Calabresi et al. *J LA State Med Soc* 2004;156:269–272	IIb	Retrospective analysis using HD-DXM in patients with ITP compared with standard therapy	6	Primary measure: to compare the timing and results of 26 episodes of HD-DXM treatment in 6 patients with no other underlying disease or complications Primary outcome: 6 patients had 9 adequate responses in the 13 episodes using HD. HD-DXM is an alternative therapy to prednisone or methylprednisone

IVIg

Citation	**LOE**	**Study design**	**Patient numbers**	**Summary**
Godeau et al. *Lancet* 2002;359:23–29	Ib	Randomised multicentre trial based on a 2 × 2 design. Untreated adults with severe ITP randomly assigned to either IV immunoglobulin or high-dose methylprednisolone (randomisation A), and then to receive either oral prednisone or placebo (randomisation B)	122	Primary measure: number of days with platelet count greater than 50×10^9/L within the first 21 days Primary outcome: platelet counts above 50×10^9/L for 18 days in 56 patients receiving IVIg and 14 days in 60 patients receiving high-dose methylprednisolone (p=0·02). 7% and 79% had platelet counts over 50×10^9/L on days 2 and 5 in

				IVIg group compared with 2% and 60%, respectively, in the high-dose methylprednisolone group (p=0·04).IVIg and oral prednisone more effective than high-dose methylprednisolone and oral prednisone in severe ITP
Spahr et al. ASH 2006:abs 3972	IIb	Retrospective review of adult hospitalised patients with clinically significant thrombocytopenia and either active bleeding, need for anticoagulation, or requirement for a surgical procedure, treated with prolonged IVIg infusion and platelets	40	Primary measure: platelet count, retreatment, bleeding, side effects, response rates Primary outcome: after 24 hours, 62.7% of patients had a platelet count >50,000/µl. Bleeding was controlled initially in all patients, and those requiring a procedure experienced no bleeding complications. 52.5% required additional treatments for recurrent or refractory ITP, and 32.5% underwent splenectomy. Combination IVIg with platelet infusions is effective for emergency treatment
Debes et al. *Pharm Drug Safety* 2007;16:1038–1047	IIb	10-year prospective observational study documenting patient characteristics, treatment parameters and the occurrence of an adverse drug reaction, using detailed case record forms	6357	Primary measure: frequency and severity of ADRs. Primary outcome: ADR occurred in 4.2% of the patients and in 0.35% of all infusions. 94.8% were non-serious, 90.2% were mild or moderate intensity. IVIg well tolerated in 10-year study including subgroup of 521 ITP patients
Chandramouli et al. *Am J Hematol* 2000;65:85–86	III	Case studies of IVIg infusion combined with platelet infusion	2	Primary measure: response measured by platelet count Primary outcome: treatment rapidly effective in increasing platelet counts in both patients. Combination IVIg with platelet infusions is effective for emergency treatment
Robak et al. ASH 2007:abs 1307	IIa	Open-label, single-arm, multicentre trial reporting on efficacy and safety of IVIg in patients with chronic ITP	57	Primary measure: platelet response rate, defined as the percentage of patients showing an increase in platelet count to ≥50 × 10^9/L within 7 days of the first infusion Primary outcome: 81% achieved defined platelet response. Median time to response was 2.5 days, with 43% of subjects responding within 1 day. Median duration of platelet response (days with platelet count ≥50 × 10^9/L) was 15.4 days. Liquid IVIg effective in patients with chronic ITP
Bussel et al. *Am J Hematol*	IIa	Two crossover studies assessing the safety and tolerability of a novel IGIV preparation	28 and 8	Primary measure: infusion-related adverse events (AEs)

2007;82:192–198		in patients with ITP		Primary outcome: headache most commonly reported infusion-related AE with incidence of 14.7%, 18.2% and 19.4% for each infusion rate of 0.08, 0.11, and 0.14 mL/kg/min, respectively. IVIg novel 'IGIV' preparation well tolerated
Siragam et al. *Nat Med* 2006;12:688–692	III	Investigation into the mode of action (MOA) of IVIg in autoimmune disease in mice	N/A	Primary measure: activation of Fcγ receptors on dendritic cells by IVIg Primary outcome: MOA of IVIg via activating Fcγ receptors on dendritic cells
Bayry et al. *Blood* 2003;101:758–765	III	Examination of the effects of IVIg on differentiation, maturation, and function of dendritic cells	N/A	Primary measure: effects of IVIg on differentiation, maturation, and function of DCs Primary outcome: MOA of IVIg via inhibition of maturation and function of dendritic cells
Spahr et al. *Am J Hematol* 2008;83:122–125	IIb	Retrospective review of patients with clinically significant ITP treated with prolonged infusions of IVIg (1 g/kg by continuous infusion over 24 hr) and concurrent platelets (1 pheresis unit every 8 hr), to determine the response rate of this therapy	40	Primary measure: platelet count, retreatment, bleeding, side effects, response rates Primary outcome: after 24 hours, 62.7% of patients had a platelet count >50,000/μl. Bleeding was controlled initially in all patients, and those requiring a procedure experienced no bleeding complications. 52.5% required additional treatments for recurrent or refractory ITPConcurrent IVIg and platelets are safe and effective at rapidly increasing platelet counts as well as for controlling bleeding symptoms.
Bussel et al. *Am J Hematol* 2001;66:172–177.	IIb	Pilot study to determine whether rhuIL-11 is an effective treatment in patients with refractory ITP	12*	Primary measure: platelet count Primary outcome: *study was terminated after 7 patients were enrolled because of toxicity and lack of efficacy. No patient achieved a count of 30,000/μl, and only 3 patients achieved (once each) a platelet count >20,000/μl. Substantial toxicity was seen although the lack of platelet response to rhuIL-11 in this study does not exclude the possibility of better effects at other doses and/or in less refractory patients.
Looney & Huggins. *Clin Haematol* 2006;19:3–25	III	Review of the development and use of IVIg	N/A	Primary measure: efficacy of IVIg in autoimmune and inflammatory conditions, the risks associated with administration of IVIg, and steps that can be taken to minimise AEs Primary outcome: practice points for the use of IVIg as a replacement therapy in primary and acquired

				humoral immunodeficiency, and as an immunomodulatory therapy in autoimmune disease and transplantation

Anti(Rh)D

Citation	LOE	Study design	Patient numbers	Summary
Newman et al. *Br J Haematol* 2001;112:10	Ib	Treatment with 75 mg/kg/d IV anti-D was compared with 50 mg/kg/d in a randomised study RhD-positive, adult, non-splenectomised patients with ITP	27	Primary measure: increase in platelet count Primary outcome: 7 out of 9 children and 9 out of 13 had platelet increases of >20 × 10^9/L by the next day following infusion of 75 mg/kg/d of IV anti-D
George et al. *Am J Hematol* 2003;74:161–169	Ib	Randomised clinical trial in adults with ITP to test the hypothesis that initial intermittent treatment with anti-D may avoid or defer the need for splenectomy	70	Primary measure: requirement for splenectomy Primary outcome: anti-D in non-splenectomised patients is as effective as maintenance therapy and may avoid splenectomy
Cooper et al. *Blood* 2002;99:1922–1927	IIa	Randomised clinical trial to investigate whether repeated infusions of anti-D may avoid the need for splenectomy following failure of initial steroid course in patients with ITP	28	Primary measure: response defined as a platelet increase of more than 20 × 10^9/L (20,000/μL) to more than 30 × 10^9/L (30,000/μL) within 7 days of treatment Primary outcome: anti-D in non-splenectomised patients is effective as maintenance therapy in 68% of patients and may avoid splenectomy
Tarantino et al. ASH 2006 (letter to editor)	IIb	Analysis of a recent prospective randomised trial in children with newly diagnosed ITP, incidence of haematuria and haemoglobinuria	91	Primary measure: haemoglobin concentration Primary outcome: pre-treatment haematuria or presumed haemoglobinuria not a predictor of haemoglobin decline
Chun et al. *Am J Hematol* 2003;74:276–279	III	Case study of adult ITP patient, incidence of acute renal failure and intravascular haemolysis	1	Primary measure: renal function, laboratory studies Primary outcome: anti-D treatment associated with intravascular haemolysis and renal failure
Genereux et al. San Diego Oct 4–6 2007:poster	III			Cases of disseminated intravascular coagulation (DIC) following anti-D for ITP may be due to existing prothrombotic condition
Genereux et al. San Diego Oct 4–6 2007:poster	III			Rate of intravascular haemolysis not correlated with increased dose at >60 μg/kg
Gaines. *Blood* 2005;106:1532–	III	Review presenting first case series of DIC associated with acute haemoglobinaemia or	6	Primary measure: anaemia, renal insufficiency, clinical and laboratory studies

1537		haemoglobinuria following anti-D IGIV administration for ITP		Primary outcome: cases of disseminated IV coagulation (DIC) following anti-D administration
Rewald & Francischetti. *Transfus Apher Sci* 2004;30:105–110	III	Case study of elderly woman with chronic pancytopenia and splenomegaly in whom anti-D caused IVH despite an 8-year tolerance, of intravascular haemolysis	1	Primary measure: intravascular haemolysis, laboratory studies Primary outcome: anti-D treatment associated with intravascular haemolysis in elderly woman
Tarantino et al. *Blood* 2007;109:5527	IV	Consideration of anti-D infusion reactions and the incidence of intravascular haemolysis (IVH) in ITP	10	Primary measure: clarify pathophysiology, diagnostic criteria and prevention of IVH Primary outcome: recommendations for the use of anti-D in ITP patients

Splenectomy

Citation	LOE	Study design	Patient numbers	Summary
Johansson et al. *Eur J Haematol* 2006;77:61–66	IIb	Long-term follow-up of efficacy and safety in adult ITP patients following splenectomy	59	Primary measure: Overall response rate (OR), PR, CR as measure by defined platelet count Primary outcome: OR: 78%, CR: 59%, PR: 19%. CR and PR patients were younger than non-responding patients at time of diagnosis (median age: 36 years vs 48 years, p=0.03) and at splenectomy (median age: 38 years vs 51 years, p=0.02)
Vianelli et al. *Haematologica* 2005;90:72–77	IIb	Long-term retrospective analysis on efficacy and safety of splenectomy in patients with ITP	345	Primary measure: CR or PR as measured by defined platelet count Primary outcome: 23% responsive patients relapsed, 80% within 48 months from splenectomy. 86% were treated with a good response. Infection and thrombosis did not significantly weigh upon the outcome of the patients. 3 patients died of haemorrhage during follow-up. Splenectomy is a safe procedure and effective in approximately two thirds of patients with chronic ITP
Ismet et al. *Clin Lab Haem* 2004;26:211–214	IIb	10-year retrospective study to investigate the efficacy and complications of splenectomy in the therapy of ITP patients	21	Primary measure: CR or PR as measured by defined platelet count Primary outcome: 12 achieved complete and 3 achieved partial haematological responses, 6 did not respond. 4 out of 6 patients responded to drugs such as azathioprine and danazol, while the other

				2 were totally refractory
Keidar et al. *Pathophysiol Haemost Thromb* 2003;33:116–119	III	Prospective data collection on ITP patients, including those with low platelet counts, following splenectomy	12	Primary measure: haematological response as measure by platelet count Primary outcome: 75% patients had good to excellent response (n=12, pre-operative platelet count <20 × 10^9/L); complication rate 33%: 1 peripancreatic haematoma, 1 subphrenic abscess that drained percutaneously and 2 involving infection (wound and urinary tract) in the third patient. Laproscopic splenectomy feasible in patients with very low platelet counts
Raedelli et al. *Haematologica* 2000;85:1040–1044	IIb	Retrospective literature study of splenectomised patients to identify potentially predictive clinical or laboratory parameters	65	Primary measure: age at diagnosis and splenectomy, time interval ITP diagnosis/splenectomy, platelet count on steroid therapy, 6 months discontinuation, pre-splenectomy, before and after IVIg. Primary outcome: univariate analysis did not reveal any significant correlation between successful splenectomy and age, sex, platelet count at diagnosis, antiplatelet antibody positivity, the site of platelet sequestration, the time between diagnosis and surgery, or the response to high IV immunoglobulin doses; probability of success greater in the patients with ≥partial pre-operative response to steroid therapy ($p<0.05$)
Shojaiefard et al. *World J Surg* 2008;32:488–493	IIb	Prospective study to determine predictive factors for the response of patients with ITP to splenectomy	31	Primary measure: response and relapse as measured by defined platelet counts Primary outcome: in open splenectomy study, older patients (>52) responded less positively than younger patients (<52) to splenectomy ($p<0.01$). Patients with sustained remission after splenectomy had significantly shorter interval of diagnosis of ITP to splenectomy ($p<0.05$) and shorter duration of steroids before splenectomy ($p<0.05$)
Cordera et al *Surgery* 2003;134:45–52	IIb	Retrospective review of medical and administrative records of post-splenectomy ITP patients between January 1995 and December 2000 to compare laparascopic splenectomy (LS) and open splenectomy	86	Primary measure: pre-operative patient characteristics, overall transfusion, post-operative complication rates, parenteral analgesia, mean post-operative stay Primary outcome: operative and anaesthesia

		(OS) clinical and economic outcomes		times, OS 167 and 201 mins; LS 119 and 151 mins, respectively, ($p<0.001$); overall transfusion and post-operative complication rates similar; LS patients required 1.2 fewer days of analgesia and tolerated a general diet 1.7 days earlier
Aledort et al. *Blood* 2006;108:abs 5536	IIb	A retrospective database analysis assessing clinical and economic burdens of ITP in a managed care population, focusing on CS use and splenectomy	770	Primary measure: health plan enrollment, ITP treatment, cost of treatment and care Primary outcome: splenectomised patients (n=90) were nearly 2.5 times more costly vs non-splenectomised patients (n=680), incurring $28,000 greater costs, increased CS use after, vs before, splenectomy
Schwartz et al. *Am J Hematol* 2003;72:94–98	IIb	Long-term retrospective study and 5-year follow-up of all patients with ITP who underwent splenectomy between 1988-1993 at 3 major medical centres	75	Primary measure: CR post-splenectomy platelet counts $>150 \times 10^9$/L without treatment; PR platelet counts $\geq 50 \times 10^9$/L without treatment and failure platelet counts $<50 \times 10^9$/L or receiving therapy after splenectomy Primary outcome: 3 patients died prior to 5-year follow-up, and 78% patients were evaluable with follow-up for ≥5 years, median 7.5 years. 8 patients had platelet counts $>150 \times 10^9$/L for 4–8.5 years before relapsing; no clear plateau attained in remission curve
Kojouri et al. *Blood* 2004;104:2623–2634	IIb	Systematic review of all case series that described 15 or more consecutive patients who had splenectomy for ITP, and that had data for one of three specified outcomes	2623	Primary measure: CR as defined by a normal platelet count following splenectomy and for the duration of follow-up with no additional treatment Primary outcome: 66% CR in adult patients with follow-up for 1–153 months; CR did not correlate with duration of follow-up ($p=0.49$)
Rossi et al. *Hematol J* 2002;3:148–152	IIb	A prospective platelet kinetic study was performed with oxine-labelled autologous platelets in adult ITP patients refractory or relapsing, following steroid treatment	93	Primary measure: platelet circulating life span, splenic platelet uptake, liver platelet uptake Primary outcome: non-ITP patients had significantly longer platelet circulating life span, lower splenic platelet uptake and higher liver platelet uptake compared with 71 patients with confirmed ITP. Thrombocytopenia was identified in 22 patients (17 with myelodysplastic syndrome and 3 with aplastic anaemia). PKS parameters not able to predict post-splenectomy relapse; relapsed patients had lower splenic/hepatic platelet uptake

				ratio (2.6 relapsed vs 4.9 persistently responsive patients; p=0.08)
Bourgeois et al. *Br J Haematol* 2003;120:1079–1088	IIb	Long-term prospective analysis of cITP patients who had splenectomy and were refractory	47	Primary measure: response to treatment as measured by defined platelet count Primary outcome: of patients refractory to splenectomy 77% of the refractory cases reached platelet counts durably >100 × 10^9/L, 9 without treatment and 27 with low-dose steroids or azathioprine; 6 (13%) remained moderately thrombocytopenic (35 × 10^9/L –100 × 10^9/L platelets); 5 patients had no response (NR) to any treatment (up to 6 regimens), remained severely thrombocytopenic (platelets <20 × 10^9/L), and 3 died from bleeding
Kubo et al. *Intern Med* 2002;41:674	III	Case study of laproscopic splenectomy, over steroid therapy in young athlete with ITP	1	Primary measure: remission as defined by platelet count, mean platelet life and platelet production Primary outcome: transient remission of disease
Budzynski et al. *Surg Endosc* 2002;16:1636	III	Case study of relapsing ITP patient where accessory spleen was removed 30 years after conventional splenectomy	1	Primary measure: response to treatment as measured by platelet count Primary outcome: patient recovered well and 2 months later steroids were discontinued while the platelet count was 251 × 10^9/L
Todorović-Tirnanić et al. *Glas Srp Aked Nauka [Med];*2005;48:119–135	IIb	A prospective platelet kinetic study using a 111In-oxinate label was performed to estimate the possibility of predicting the splenectomy response in patients with chronic ITP	34	Primary measure: platelet life span, production, sequestration index and sequestration/destruction site determination Primary outcome: platelet labelling makes the clinicians' decision to perform a splenectomy easier

Post-splenectomy infections

Citation	LOE	Study design	Patient numbers	Summary
Kaplinsky et al. *Pediatr Blood Cancer* 2006;47:740–741	III	Literature review of prophylactic antibiotic treatment post-splenectomy	N/A	Primary measure: incidence of post-splenectomy infection Primary outcome: the issue of prophylactic antibiotic therapy in these patients remains inconclusive in post-splenectomy patients
Webb et al. *J Fam*	IIb	Systematic review of vaccines indicated	N/A	Primary measure: Antibody levels following

Pract 2006;55:711–712		post-splenectomy		immunisation with vaccines Primary outcome: Pneumococcal, meningococcal, and *Haemophilus influenzae* (Hib) vaccinations are indicated for patients after splenectomy
O'Donnell et al. *Ir J Med Sci* 2004;173:136–140	IIb	Retrospective chart review on impact of guidelines on post-splenectomy infection	100	Primary measure: incidence of post-splenectomy infection Primary outcome: overwhelming post-splenectomy infection (OPSI) has a 50–70% mortality rate and carries a lifetime risk for the asplenic patient. 20% discharged without vaccination, prophylactic antibiotics not prescribed in 53%. Overall mortality 12%
El-Alfy & El-Sayed. *Hematol J* 2004;5:77–80	III	Study to examine the impact of patients' knowledge and compliance on the prevention of overwhelming post-splenectomy infection	318	Primary measure: patient questionnaire to assess the degree of knowledge and compliance, and their role in the prevention of post-splenectomy risks Primary outcome: OPSI occurred among 5.7% (n=18) of patients. Lifelong antibiotic prophylaxis remains of disputed value since no OPSI was recorded more than 10 years post-splenectomy
Balmer et al. *Infect Immun* 2004;72:332–337	IIb	A study of the immune response of asplenic individuals to meningococcal serogroup C conjugate (MCC) vaccine	130	Primary measure: geometric mean titer (GMT) of bactericidal antibody in serum (SBA) following immunization with the MCC vaccine Primary outcome: 93% of asplenic individuals achieved a titer of ≥8 following MCC vaccination. It is recommended therefore that following vaccination of asplenics, either the level of functional antibody should be determined, with a second dose of MCC vaccine offered to non-responders, or 2 doses of MCC should be routinely offered
de Montalembert & Lenoir et al. *Ann Hematol* 2004;83:18–21	IV	Assessment of antibiotic prevention of pneumococcal infections in asplenic patients	(152)	Primary measure: questionnaire to 104 physicians to assess the risk of pneumococcal infections in their asplenic patients Primary outcome: pneumococcal vaccination and daily oral administration of penicillin V are recommended to prevent infections, but asplenic patients do not generally continue treatment and so there is an urgent need to improve their management

High-dose methyl-prednisolone

Citation	LOE	Study design	Patient numbers	Summary
Alpdogan et al. *Br J Haematol* 1998;103:1061–1063*	IIa	Non-randomised study comparing the efficacy of conventional and high-dose prednisolone as first-line treatment in adult ITP	57	Primary measure: CR platelet count to >100 × 10^9/L, remission platelet count >50 × 10^9/L. Complete maintenance of platelet count at >100 × 10^9/L for 2 months or more without taking any medication. Complete remission persisting until the last follow-up (at least 6 months), accepted as persistent complete remission. Primary outcome: patients in the HDMP arm responded rapidly (4.7 v 8.4 days), with a higher RR (80% v 52.7%), and without severe side effects. One quarter of the patients (3/12) who were non-responsive to CDP achieved complete remission when treated with HDMP
Kuku et al. *Eur J Haematol* 2005;74:271–272	III	Letter to the editor: prospective study of early and long-term results of oral high-dose prednisone therapy in ITP patients	30	Primary measure: response as measured by platelet count >50 × 10^9/L Primary outcome: response rate achieved in 95% of patients receiving HDMP as first-line therapy, 80% as second-line therapy. Oral HDMP treatment more efficient than conventional dose prednisolone in cases of bleeding and pre-urgent surgery, when platelet number should be raised quickly

Vinca-alkaloid

Citation	LOE	Study design	Patient numbers	Summary
Szczepanik et al. *Int J Lab Hematol* 2007;29:347–351	IIb	To evaluate the efficacy of vinca alkaloids (VAs) in preparing adult corticosteroid-refractory chronic ITP patients for splenectomy	12	Primary measure: increase in platelet level to at least 80 × 10^9/L following VA treatment Primary outcome: VAs increased platelets to a level sufficient for safe splenectomy in 9 patients
Boruchov et al. *Blood* 2007;100:3526–	IIb	Study to assess effect of 3- or 4-drug combinations including IVIg, IV methylprednisolone, VAs and/or IV anti-D in	35	Primary measure: increase in platelet count following combination treatment for acute induction and long-term maintenance therapy

3531		patients unresponsive to IVIg or high-dose steroid treatment, requiring an acute increase in platelet count for surgery or ongoing haemorrhage, as well as long-term maintenance treatment		Primary outcome: IV combination treatment caused an acute increase in platelet count to a level greater than 30 × 10^9/L in 71% of chronic refractory ITP patients. Two thirds of the patients given maintenance therapy achieved stable platelet counts greater than 50 × 10^9/L

Danazol

Citation	LOE	Study design	Patient numbers	Summary
Maloisel et al. *Am J Med* 2004;116:590–594	IIa	Prospective, long-term, cohort study to identify the effectiveness of danazol in ITP patients	57	Primary measure: CR ie platelet count increased to ≥150 × 10^3/μL that was sustained for ≥2 months, PR ie platelet count increased above 50 × 10^3/μL that was sustained for ≥2 months. These patients defined as responders Primary outcome: 38 patients experienced a partial or CR to therapy (67%), among whom 27 (46%) remained in remission at a median (±SD) of 119±45 months. Danazol effective for management of chronic refractory ITP or patients with contra-indications to steroids or splenectomy
Nakhoul et al. ASH 2006:abs 3989	IIa	Single arm, non-randomised, phase II trial, utilising a single stage design to compare rates of discontinuance of anti-Rh(D) at the end of 1and 2 years following combination treatment with danazol	5	Primary measure: response to combination treatment as measured by number of anti-Rh(D) infusions required to sustain response Primary outcome: danazol in combination with anti-D may provide effective treatment
Andres et al. EHA 2007:abs 1317	IIb	Retrospective study conducted among 30 elderly patients with ITP	30	Primary measures: clinical characteristics (blood count, bleeding, platelet count), therapies, response rates, side effects Primary outcome: danazol may be effective in elderly patients with refractory ITP: only 5 patients treated

Cyclosporin A

Citation	LOE	Study design	Patient numbers	Summary

Emilia et al. *Blood* 2002;99:1482–1485	IIa	Report describing long-term treatment with CyA and follow-up in adult patients with resistant ITP	12	Primary measure: CR platelet count in normal range for at least 3 months after CyA treatment discontinued. PR platelet count between 80 and 120 × 10^9/L for at least 3 months while patient not receiving CyA. Response to maintenance therapy (MTR) platelet count in normal range during continuous administration of CyA. NR platelet count that did not rise above 40 × 10^9/L Primary outcome: clinical improvement observed in 10 patients (83.3%), of which 5 had a CR, 5 had a CR to maintenance therapy and 1 had a PR. Most patients with a response (60%) showed long-term remission (mean 28.6 months) following discontinuation of treatment. Cyclosporin A is effective as long-term salvage treatment for patients with refractory ITP
Kappers-Klunne & van't Veer. *Brit J Haematol* 2001;114:121–125	IIb	Prospective study of the efficacy of Cyclosporin A (CyA) in patients with chronic ITP refractory to corticosteroids or splenectomy	20	Primary measure: feasibility of intensive immunosuppression using combination of CyA and corticosteroids to induce remission in ITP patients refractory to corticosteroids before or after splenectomy; CR platelet count 110 × 10^9/L for >12 weeks Primary outcome: overall response rate 55%; CyA treatment does not avoid, but postpones, splenectomy in chronic ITP patients refractory to corticosteroids. CyA is effective in patients with corticosteroid and splenectomy-refractory ITP, but treatment toxicity is high

Dapsone

Citation	**LOE**	**Study design**	**Patient numbers**	**Summary**
Sharma et al. ASH 2006:abs 1073	IIa	Efficacy report of dapsone in consecutively treated patients who had continued to be symptomatic despite adequate steroid therapy	46	Primary measure: response to treatment as measured by disappearance of purpura and significant rise in platelet count Primary outcome: dapsone was splenectomy-sparing in steroid resistant patients
Vancine-Califani et	IIb	Retrospective evaluation of the results of	58	Primary measure: overall and definitive avoidance

al. ISTH 2007:abs P-W-313		dapsone treatment in ITP patients who failed first-line therapy with steroids		of splenectomy because of significant and sustained rise in platelet counts (>50,000/ μL) clearly attributed to dapsone treatment Primary outcome: dapsone treatment in steroid-dependent or refractory ITP may avoid immediate splenectomy

Rituximab

Citation	LOE	Study design	Patient numbers	Summary
Arnold et al. *Ann Intern Med* 2007;146:25–33	IIa	Systematic literature review of the efficacy and safety of rituximab for the treatment of adults with ITP	306	Primary measure: platelet count response, toxicities, dose, previous treatments, baseline platelet count, duration of ITP, study design, sources of funding Primary outcome: rituximab resulted in overall platelet count response in 62.5% adults with ITP. However, findings also reported toxicities, including death in 2.9% of cases
Ramanarayanan et al. ASH 2006	IIa	Review of the current available literature and meta-analysis on efficacy and safety of rituximab in the treatment of refractory/relapsed ITP	299	Primary measure: disease duration, rituximab toxicity, characteristics of responders, CR platelet count of at least 100,000–150,000, PR platelet count >50,000 and <100,000 Primary outcome: 55% of patients with relapsed/refractory ITP showed a response to rituximab
Zaja et al. ASH 2007:abs 1305	IIa	Prospective study of adult patients with previously treated, active and symptomatic ITP, treated with rituximab	28	Primary measure: OR platelet count ≥50 × 10^9/L, CR platelet count ≥100 × 10^9/L and discontinuation of steroid therapy, if present). Time to response platelet count ≥50 × 10^9/L, time to CR platelet count ≥100 × 10^9/L and the duration of response Primary outcome: effective treatment with low-dose rituximab (100 mg IV weekly) but with longer time to response vs standard dose
Cooper et al. *Br J Haematol* 2004;125:232–239	IIa	Study assessing the efficacy and safety of rituximab in adults with chronic ITP	57	Primary measure: CR platelet count >150 × 10^9/L and PR platelet count 50–150 × 10^9/L Primary outcome: rituximab effective in patients with chronic refractory ITP; 54% responded; 32% long-term response. 18 achieved CR and 13

				achieved PR
Stasi et al. *Blood* 2007;110:2924–2930	IIa	Investigation into the changes of different peripheral blood T-cell subsets, the apoptosis profile, and changes of T-cell receptor (TCR) ß-variable (VB) region gene usage of $CD4^+$ and $CD8^+$ T-cell subpopulations following rituximab therapy in ITP patients	30	Primary measure: changes in peripheral blood Th and Tc subsets by analysis of intracellular cytokines, the apoptosis profile of different T-cell subsets, and changes of TCR VB gene patterns Primary outcome: rituximab mechanism of action associated with changes in T-cell compartment
Patel et al. ASH 2006:abs 479	IIa	Study assessing the long-term efficacy of rituximab in patients with chronic ITP	31	Primary measure: duration of response to treatment, relapse rate, CR platelet count >150 × 10^9/L, PR platelet count 30 to 150 × 10^9/L Primary outcome: long-term benefits of rituximab, responses observed for up to 2.5 years
Müller et al. EHA 2007:abs 1330	IIa	Evaluation of the effect of rituximab in remission of chronic immune cytopenias	15	Primary measure: CR platelet count >150 × 10^9/L, PR platelet count 50 to 150 × 10^9/L Primary outcome: 13 patients with chronic refractory ITP responsive to rituximab
Santoro et al. ASH 2006:abs 3979	IIa	Investigation into the efficacy of rituximab in patients with resistant ITP	14	Primary measure: CR platelet count >150 × 10^9/L, PR platelet count >50 <150 × 10^9/L, minimal response (MR), >20 ≤50 × 10^9/L; NR ≤20 × 10^9/L, relapse Primary outcome: 7 responses (2 CR, 4 PR, 1 MR; 50%) and 7 NR (50%) were observed 1 month after treatment with rituximab. Rituximab effective in patients with chronic refractory ITP
Godeau et al. ASH 2006:abs 478	IIa	Multicentre, prospective, open-label, single-arm, phase II study assessing the safety and efficacy of rituximab in adults with chronic ITP	60	Primary measure: platelet count ≥150 × 10^9/L with at least a 2-fold increase of the initial value at 1 year after the first rituximab infusion Primary outcome: success was achieved in 40% (24/60 patients). Among the 24 long-term responders, platelet count at 1 year was ≥150 × 10^9/L in 18 and between 50 and 150 × 10^9/L in 6. Rituximab was effective and splenectomy-sparing in patients with chronic ITP
Giagounidis et al. *Eur J Haematol* 2002;69:95–100	IIa	Prospective pilot study to evaluate efficacy of the anti-CD20 monoclonal antibody rituximab, in relapsed ITP	12	Primary measure: CR normalisation of thrombocyte count for at least 30 days. PR an increase of thrombocytes to above 30,000 μL^{-1} for at least 30 days. Minor response (MR) any increase above 30,000 μL^{-1} for less than 30 days but more than 10 days. NR failure to achieve any of the above

				responses. Patient outcome: 5 patients (41%) achieved CR, 2 (17%) PR, and 2 MR (overall response rate 75%, median follow-up of responders 320 days). Rituximab was effective in patients with relapsed ITP
Zaja et al. *Haematologica* 2002;87:189–195	IIa	Study to assess the effects of rituximab in AIHA and thrombocytopenia	4	Primary measure: OR platelet count ≥50 × 10^9/L, CR platelet count ≥100 × 10^9/L and discontinuation of steroid therapy, time to response, time to CR, duration of response Primary outcome: All patients achieved B-cell depletion, OR and CR were achieved in 21/28 (75%) and 12/28 (43%) patients, respectively. Rituximab was effective in patients with chronic refractory ITP
Provan et al. *Haematologica* 2007;92:1695–1698	IIb	Retrospective analysis of consecutive patients with various autoimmune cytopenias who failed to respond to conventional treatments now treated with rituximab	11	Primary measure: CR platelet count >150 × 10^9/L on 2 consecutive occasions, PR platelet count 50 to 150 × 10^9/L on 2 consecutive occasions, duration of response from the day of the initial infusion to the first time of relapse (platelet count <30×10^9/L) or to time of analysis Primary outcome: effective treatment with low-dose rituximab (100 mg weekly 4 times), complete and durable response observed in 4 out of 7 (57%) patients
Dabak et al. ASH 2007:abs 1306	IIb	Retrospective chart review of patients with ITP treated with rituximab	29	Primary measure: CR platelet count >150 × 10^9/L, PR platelet count >50 <150 × 10^9/L provided response sustained for 12 months Primary outcome: 18 patients (62%) achieved CR, 2 (7%) achieved PR, with an overall response rate (ORR) of 69%; 6 (21%) did not respond. Average time to response 5 weeks. Rituximab was effective and splenectomy-sparing in patients with chronic ITP
Tsiora et al. EHA 2007:abs 1399	IIb	Retrospective evaluation to examine the clinical features, laboratory findings and effects of different treatment modalities in patients with ITP	59	Primary measure: clinical features (bruising, bleeding), laboratory findings (antibodies) Primary outcome: 33 patients (56%) asymptomatic at diagnosis and thrombocytopenia found on routine visit to physician. 13 patients (22%) presented with easy bruising and/or petechiae, 12

				(20%) with minor bleeding, and 1 with severe intracerebral hemorrhage. 31 patients (17%) had a positive autoimmune profile. Rituximab was effective in patients with chronic refractory ITP
Stasi et al. *Blood* 2002;99:3872	IIb	Retrospective study observing patterns of response in rituximab therapy in chronic ITP patients	7	Primary measure: CR platelet count >100 × 10^9/L, PR platelet count >50 <150 × 10^9/L Primary outcome: 4 patients achieved CR, 2 achieved PR. Variability of response to rituximab, early and late responders (up to 6 weeks post-treatment)
Dierickx et al. ASH 2007:abs 1737	III	Multicentre registry analysis of patients given rituximab in the setting of ITP or AHAd	23	Primary measure: ITP CR platelet count >100,000/μL without immunosuppressive therapy and PR platelet count 50–100,000/μL without immunosuppressive drugs. AHA CR, normal haemoglobin in absence of haemolysis, and PR, a 2g increase of the haemoglobin concentration. Primary outcome: 13 ITP achieved CR, 2 ITP achieved PR, 15 AHA achieved CR and 20 AHA achieved PR. No significant correlation between response and sex, age, prior splenectomy, platelet count or haemoglobin concentration when rituximab was started in ITP and AHA patients
Tanaka et al. ASH 2006:abs 1077	III	Case reports of chronic refractory ITP patients treated with single-dose rituximab	5	Primary measure: response to treatment measured by platelet count Primary outcome: 2 patients responded after 7 month interval, 1 within 24 days, 1 within 20 days, 1 after 45 days. Single-dose treatment was effective in some cases of refractory ITP and effect may continue to provide long-term remission
Riksen et al. *Neth J Med* 2003;61:262–265	III	Case study on patient with frequently relapsing ITP treated with rituximab	1	Primary measure: normalisation of platelet count Primary outcome: normalisation of platelet count with a platelet count of 200–250 × 10^9/L following infusion with rituximab; no side effects. Rituximab may be effective in steroid-responsive frequently relapsing ITP
Koulova et al. *Am J Hematol* 2005;78:49–54	III	Case study of rituximab treatment in 1 ITP patient and 2 thrombotic thrombocytopenic purpura (TTP) patients	3	Primary measure: response to rituximab as measured by platelet count Primary outcome: after several weekly doses of rituximab, all patients achieved sustained remission of their autoimmune disease. Rituximab

				was effective in patient with refractory ITP and TTP
Luzzatto et al. *Clin Appl Thromb Hemostasis* 2006;12:120–121	III	Case study of severe, acute ITP patient treated with rituximab	1	Primary measure: response to treatment as measured by platelet count Primary outcome: platelet count rose after third injection and patient subsequently fully recovered and stabilised with a follow-up of 16 months to date. Rituximab was effective in patient with acute primary ITP
Latifzadeh et al. *Clin Appl Thromb Hemostasis* 2006;12:489–492	III	Case study of chronic, refractory ITP patient treated with rituximab	1	Primary measure: response to treatment as measured by platelet count Primary outcome: after 2 months' rituximab treatment platelet levels rose to acceptable level, sustained at 18 months. Rituximab was effective in patient with chronic refractory ITP
Fianchi et al. *Ann Hematol* 2007;86:225–226	III	Case study of ITP patient treated with rituximab, presenting with infectious complications	1	Primary measure: response to treatment as measured by platelet count and clinical and laboratory studies Primary outcome: rituximab was associated with severe infectious complications
Kuwana et al. *Am J Hematol* 2007;82:846–848	III	Case study of ITP patient treated with rituximab becoming refractory at 13 weeks following initial response	1	Primary measure: appearance of plasma cells producing anti-GPIIb/IIIa antibodies Primary outcome: appearance of plasma cells producing anti-GPIIb/IIIa antibodies, possible mechanism of rituximab resistance
Saouli et al. ASH 2006:abs 3968	III	Case studies of relapsed and resistant ITP patient treated with rituximab	3	Primary measure: satisfactory platelet response with platelets over 100×10^9/L Primary outcome: rituximab was effective in patients with chronic refractory and relapsed ITP
Narang et al. *Am J Hematol* 2003;74:263–267	III	Series of case studies of autoimmune, refractory thrombocytopenia treated with rituximab	6	Primary measure: satisfactory platelet response Primary outcome: satisfactory platelet response achieved in 5 of 6 patients. Maximum responses reached between 3 and 8 weeks
Arguinano et al. EHA 2007:abs 1151	III	Single-centre case studies of eight patients treated with rituximab for refractory ITP	8	Primary measure: response platelet count of at least 50×10^9/L achieved in the 120 days followinf first rituximab administration, in the absence of bleeding symptoms and no administration of other effective therapy in that period of time Primary outcome: responses achieved in 6 of 8 patients. Median time to response 38 days, ranging from 12 to 68 days. 1 non-responder treated with

				splenectomy; other remained unresponsive
Serpa et al. *J Thromb Haemost* 2007;5:abs P-W-312	III	Case study of ITP patient with bleeding symptoms treated with rituximab	1	Primary measure: clinical and laboratory evaluations Primary outcome: rituximab (375 mg/m^2) not effective, developed sepsis, CNS bleeding and died
Narat et al. *Haematologica* 2005;90:1273–1274	III	Case studies of refractory autoimmune cytopenia patients (AIHA and chronic ITP) treated with rituximab	6	Primary measure: AIHA CR resolution of both anaemia (Hb ≥13 g/dL [males], ≥12 g/dL [females]) and signs of haemolysis following no therapy for at least 4 weeks after rituximab treatment. PR a stable increase in haemoglobin level of at least 2 g/dL and discontinuation of concomitant therapy. CR and PR in ITP resolution of bleeding with a platelet count of >150×10^9/L and >50×10^9/L, respectively, on 2 consecutive occasions following no concomitant therapy 4 weeks after completion of rituximab Primary outcome: overall response rate 64% in the AIHA group (3 CR and 4 PR) and 83% in the ITP group (4 CR, 1 PR). Responses in AIHA patients with underlying lymphoproliferative disorders receiving rituximab with chemotherapy generally better sustained, whereas responses in ITP were often transient
Zaja et al. ASH 2008; abs 1	Ib	A prospective randomized, multicentre, Phase III study comparing treatment with dexamethasone alone vs dexamethasone plus rituximab in adult patients with previously untreated ITP and a platelet count $\leq 20 \times 10^9$/L	101	Primary measure: to compare the sustained response (SR), i.e. platelet count ≥50 x 10^9/L at month + 6 of treatment Primary outcome: patients administered combination therapy had significant advantages in terms of sustained response (ITT population: 63% vs 36% in patients with platelet count ≥50 x 10^9/L; pp=0.004) compared with dexamethasone-only treated patients
Godeau et al. *Blood* 2008;112:999–1004	IIb	Prospective multicentre open-label, single-arm to assess rituximab efficacy and safety in adult splenectomy candidates with ITP	60	Good 1-year responses were obtained in 40% of the patients. 33.3% had good 2-year responses and 6.7% had sustained platelet counts of 30 × 10^9/L or more without treatment. 60% patients failed to respond; 42% underwent splenectomy. Based on these results, rituximab was an apparently safe and effective splenectomy-avoiding

				option in some adults with chronic ITP

Campath-1H

Citation	LOE	Study design	Patient numbers	Summary
Willis et al. *Br J Haematol* 2001;114:891–898	III	Case study patients with severe and life-threatening autoimmune cytopenias resistant to standard immunosuppression who were treated with the monoclonal antibody Campath-1H.	21 (n=9 with ITP)	Campath-1H was administered at a dose of 10 mg per day as an intravenous infusion for 10 d. Fifteen patients responded of which six had a sustained response. Relapse occurred in eight patients after treatment
Ammatuna et al. *Eur J Haematol* 2004;73:225–226	III	Case study of steroid-resistant autoimmune ITP in a patient with low tumour burden CLL	1	Primary measure: platelet count, clearance of neoplastic cells Primary outcome: treatment produced rapid clearance of neoplastic cells from blood and bone marrow, platelet count increased to normal levels after 12 weeks. Successful treatment of steroid-resistant ITP associated with CLL

Mycophenolate mofetil

Citation	LOE	Study design	Patient numbers	Summary
Hou et al. *Eur J Haematol* 2003;70:353–357	IIb	Study to induce durable response in patients with refractory ITP by applying mycophenolate mofetil (MMF)	21	Primary measure: CR double platelet counts ≥100 × 10^9/L, 12 weeks after MMF administration. PR platelet count 50 × 10^9/L ≤double platelet counts <100 × 10^9/L, 12 weeks after MMF administration. MR double platelet counts <50 × 10^9/L with increase in platelet count ≥20 × 10^9/L, 12 weeks after MMF administration. NR: double platelet counts <50 × 10^9/L with increase in platelet count <20 × 10^9/L, 12 weeks after MMF administration Primary outcome: overall response rate was 62% (13 of 21), including 24% CR, 29% PR, and 10% MR. Response rates for non-splenectomised and splenectomised ITP patients were 64% and 57%, respectively. Effective in refractory ITP,

				resistant to steroids and splenectomy
Provan et al. *Am J Haematol* 2006;81:19–25	IIb	Pilot study to determine whether MMF is an effective single-agent treatment for refractory ITP	18	Primary measure: efficacy defined as sustained platelet increase to a level >50 × 10^9/L Primary outcome: sustained platelet increase in 7 patients, 3 had intermittent thrombocytopenic episodes while continuing medication. MMF effective as combination protocol but not as sole agent for patients with refractory ITP
Zhang et al. *Acta Pharmacol Sin* 2005;26:598–602	IIb	Long-term study to determine whether MMF has beneficial effects on refractory ITP in patients resistant to corticosteroid and/or splenectomy and chemical therapy	20	Primary measure: CR, thrombocyte count >300×10^9/L, and blood platelet count >100×10^9/L. No bleeding for at least 3 months and no relapse for 2 years. PR, blood platelet count >50×10^9/L or 30×10^9/L higher than that before MMF treatment. No bleeding for 2 months. MR, increase in blood platelet count not exceeding 30×10^9/L after MMF treatment. Bleeding symptoms were improved for 2 weeks. No response, blood platelet was unchanged and bleeding symptoms were neither improved or worsened Primary outcome: 80% had responses to MMF treatment; CR 45%; PR 20%; MR: 15%. Therapy for a period of 8 to 16 weeks with median dose MMF was valuable for treating refractory ITP
Kotb et al. *Eur J Haematol* 2005;75:60–64	IIb	Retrospective: prospective open preliminary study to evaluate the efficacy and safety of mycophenolate mofetil in patients with AIHA and AITP	13	Primary measure: Improvement of platelet/haemoglobin levels, reduction of previously given drugs Primary outcome: AITP patients, an overall response of 78% was observed; all AITP patients with associated auto-antibodies responded to MMF, only 50% of patients without associated antibodies were responders

Romiplostim

Citation	LOE	Study design	Patient numbers	Summary
Kuter et al. *Lancet* 2008;371:395–403	Ib	Assessment of the long-term administration of romiplostim in splenectomised and non-splenectomised patients with ITP in 2	125	Primary measure: durable platelet response (platelet count ≥50 × 10^9/L during 6 or more of the last 8 weeks of treatment) and treatment safety

		parallel trials		Primary outcome: efficacy of romiplostim (R) in splenectomised (n=63) and non-splenectomised (n=62) patients, durable platelet response achieved by 16/42 R splenectomised patients vs 0/21 placebo and 25/41 R non-splenectomised patients vs 1/21 given placebo
Bussel et al. *N Eng J Med* 2006;355:1672–1681	Ib	Phase I–II study administering AMG 531 to patients with ITP evaluating safety and efficacy	24 and 21	Primary measure: Assessment of safety of AMG 531. Platelet count secondary measure. Primary outcome: No AEs could be attributed to AMG 531 during treatment period. Platelet count of at least 50,000 per mm^3 was achieved in 7/12 patients
Newland et al. *Brit J Haematol* 2006;135:547–553	Ib	Open-label, phase I–II, multicentre trial to evaluate the safety of AMG 531	16	Primary measure: assessment of safety of AMG 531, clinical laboratory studies, antibody assays Primary outcome: 2 patients experienced serious AEs related to AMG 531 (severe headache and elevated serum lactic dehydrogenase; thrombocytopenia). AMG 531 was well tolerated at 30, 100 and 200 µg SC doses
Kumagai et al. *J Clin Pharmacol* 2007;47:1489–1497	Ib	Double-blind, phase I randomised study evaluating the safety, pharmacodynamics, and pharmacokinetics of AMG 531	30	Primary measure: safety of AMG 531, platelet aggregation, platelet counts Primary outcome: no enhancement or reduction in platelet aggregation detected in samples collected from subjects treated with AMG 531 compared with either pre-treatment or placebo samples. Overall, AEs similar between the AMG 531 and placebo groups. Treatment-related AEs (headache, 'feeling hot', migraine without aura, and/or malaise) were reported for 5 of 24 subjects treated with AMG 531. Platelet counts were raised and AMG 531 was well tolerated
Pullarkat et al. ASH 2007	Ib	Report on efficacy and safety of IVIg or anti D in splenectomised and non-splenectomised patients in combination with AMG 531 treatment from 2 randomised, double blind, placebo-controlled phase III studies	125	Primary measure: % of patients requiring Ig intervention in each month of treatment and the age and sex-adjusted 24-week cumulative probability of Ig use. Primary outcome: In 24-week study period, there were 19 Ig administrations among 83 AMG 531 patients, and 68 Ig administrations among 42 placebo patients. Cumulative probability of incurring Ig use in 24 weeks was 0.51 (SE: 0.08)

				for placebo arm and 0.13 (SE: 0.04) for AMG 531 arm, with a hazard ratio of 5.31 (95% CI: 2.55–11.06, p<0.001). Reduction in IVIg or anti-D in patients receiving romiplostim (expansion of data from Kuter *Lancet* paper)
Kuter et al. ASH 2006:abs 476	IIa	Long-term open label extension study investigating efficacy and safety of romiplostim in thrombocytopenic patients with ITP	104	Primary measure: AEs, mean platelet count Primary outcome: AE profiles similar for intervals of weeks 1–24 vs 25–48 and beyond. Most frequent AEs were headache (2.0 per 100 weeks of subject exposure for weeks 1–24 vs 1.7 for weeks 25–48), upper respiratory infection (1.3 vs 0.8) and fatigue (0.9 vs 1.0). 4 patients had serious treatment-related AEs. Mean platelet count and mean dose remained stable for weeks 24–48. Mean platelet count was 100 × 10^9/L during weeks 1–24 and 131 × 10^9/L during weeks 25–48
Bussel et al. ASH 2007:abs 568	IIa	Long-term (2 year) open label extension study investigating efficacy and safety of romiplostim in ITP patients	136	Primary measure: AEs, platelet response, clinical and laboratory studies Primary outcome: most frequently reported AEs were headache (31%), contusion (27%), fatigue (24%), diarrhoea (24%), epistaxis (23%), nasopharyngitis (21%) and arthralgia (20%). 112 patients (82%) achieved a platelet response
Shirasugi et al. ASH 2007:abs 1308	IIa	Open-label phase II safety study conducted to identify the appropriate starting dose of AMG 531 for treatment of chronic ITP	12	Primary measure: cohort dose escalation to be stopped in the event of an observed platelet count >1000 × 10^9/L, AEs Primary outcome: Proportion of patients achieving a platelet response (doubling of baseline counts and ≥50 × 10^9/L) was greater in cohorts receiving higher doses of AMG 531. Most common treatment-related AE in the cohort phase was headache (25%), and in the treatment continuation phase arthralgia, contact dermatitis, and malaise (each 20%). Romiplostim was well tolerated and produced a dose-responsive increase in platelet counts
Newland et al EHA 2008:abs 0945		Ongoing open-label extension study to evaluate the safety and efficacy of romiplostim in adult patients with chronic ITP	143	Primary measure: platelet response (platelet count >50 × 10^9/L and double baseline) Primary outcome: platelet response achieved by 87% of patients overall. Romiplostim was well

				tolerated and produced rapid and sustained increases in platelet counts allowing patients to discontinue or reduce concurrent ITP medications
Wang et al. *Clin Pharmacol Ther* 2004;76(6):628–638		Evaluation of the tolerability, pharmacodynamics, and pharmacokinetics of AMG 531 after a single intravenous (IV) or subcutaneous (SC) injection in healthy subjects	48	Primary measure: the pharmacodynamic response of AMG 531 was measured as the elevation in platelet counts; AMG 531 serum levels were determined by use of a validated enzyme-linked immunosorbent assay. Single IV or SC administration of AMG 531 induced a dose-dependent increase in platelet count in healthy subjects, with peak platelet count being achieved on Days 12 to 16. No serious or life-threatening adverse events reported in this study
Kuter et al. ASH 2008; abs 402	Ib	Open-label extension study to evaluate the efficacy and safety of romiplostim in adult patients with chronic ITP who have a platelet counts ≥50 × 10^9/L	142	Primary measure: Romiplostim was administered subcutaneously once weekly with dose adjustments to maintain a platelet count of 50-250 × 10^9/L Primary outcome: Platelet counts were increased from baseline by $\geq 20 \times 10^9$/L more than 80% of the time in 54% of patients and more than 50% of the time in 73% of patients. Platelet counts remained above 20×10^9/L more than 90% of the time in 67% of patients and more than 50% of the time in 94% of patients. The patient incidence of bleeding events both of any severity and of clinical significance (≥Grade 3) declined over time
Kuter.*Blood* 2007;109:4607–4616	IV	Review of second-generation thrombopoietic growth factors that are potent stimulators of platelet production and are devoid of any apparent immunogenicity	N/A	Primary measure: consider existing and new thrombopoietic growth factors, their structure and function, their utility in treating thrombocytopenic disorders, and the potential risk of thrombopoietic growth factor therapy Primary outcome: 2 thrombopoietic agents, AMG 531 and eltrombopag, are currently in the final phases of clinical development and have been shown to be highly effective in the treatment of ITP

Eltrombopag

Citation	**LOE**	**Study design**	**Patient**	**Summary**

			numbers	
Bussel et al. ASH 2007:abs 1299	Ib	4 randomised, placebo-controlled trials investigating safety	117, 114, 180 and 74	Primary measure: safety following once-daily dosing; AEs, ophthalmological examination results, clinical laboratory data, physical examination, vital signs and ECGs frequently assessed Primary outcome: no apparent association between the administration of different doses of eltrombopag and AE reports
Bussel et al. *N Eng J Med* 2007;357:2237–2247	Ib	Randomised study investigating efficacy and safety of eltrombopag in patients with relapsed/refractory ITP	118	Primary measure: platelet count of 50,000 or more per mm^3 on day 43 Primary outcome: platelet count of at least 50,000 per mm^3 was achieved in 28%, 70%, and 81% of patients, on doses of 30, 50 and 75 mgs, respectively
Jenkins et al. *Blood* 2007;109:4739–4741	Ib	Phase I placebo-controlled dose-ranging clinical trial in healthy subjects	73	Primary measure: safety, tolerability, pharmacokinetics, and pharmacodynamics of eltrombopag, when administered as a once-daily oral dose Primary outcome: PK of eltrombopag dose-dependent and linear; platelet counts increased in a dose-dependent manner. AEs did not differ among healthy human subject treatment groups, including placebo, and were not dose related
Provan et al. ASCO 2006;24:abs 18596	Ib	Randomised placebo-controlled parallel group trials presenting safety and tolerability data. Dose 3–75 mg for up to 6 weeks	219	Primary measure: safety and tolerability data for eltrombopag in healthy subjects (n=115) and ITP patients (n=104). Assessment of AEs and clinical laboratory parameters, including ECGs and platelet function. Primary outcome: no apparent relationship between eltrombopag dose and safety measures
Bussel et al. ASCO 2006;24:abs 8602	Ib	Two randomised, placebo-controlled trials. 5–75 mg. Efficacy data of eltrombopag in healthy (n=73) and phase II ITP patients (n=95)	168	Primary measure: the primary efficacy endpoint in the phase II ITP trial was the proportion of subjects with a platelet count >50 × 10^9/L after 6 weeks of dosing Primary outcome: healthy subjects; dose-dependent increase in the platelet counts. Mean maximal platelet count increases were 24.1, 42.9 and 50.4% at 30, 50 and 75 mg, respectively. ITP patients; platelet counts increased from <30 to >50 × 10^9/L in 28, 67 and 86% of patients receiving

				eltrombopag 30, 50 and 75 mg, respectively.
Bussel et al. EHA 2007:abs 758	Ib	Two multicentre, double-blind, placebo-controlled, randomised clinical trials including patients with chronic ITP in phase II and III were analysed. In both studies, subjects with platelet counts <30,000/μL received different doses of eltrombopag, an oral thrombopoietin-receptor agonist, or placebo for up to 6 weeks and were observed for 6 weeks after discontinuation of study treatment	231	Primary measure: bleeding assessed weekly during treatment and biweekly after discontinuation of study drug using the WHO bleeding. Severe bleeding events defined as any cerebral bleeding, or any Grade 3 or Grade 4 bleeding event. Primary outcome: reduction in severe bleeding following treatment; 9/231 patients either refractory to eltrombopag or on placebo, experienced a total of 9 severe or life-threatening bleeding episodes including 3 intracranial haemorrhages (n=117 and n=114)
Bussel at al. EHA 2007b:abs 0390	Ib	Global, randomised, double-blind, placebo-controlled, phase III trial, studying the safety and efficacy of eltrombopag 50 mg once daily for up to 6 weeks. Dose escalation to 75 mg (or matching placebo) was allowed after 3 weeks in subjects whose platelet count continued to be <50,000/μL.	114	Primary measure: proportion of patients with a platelet count >50,000/μL after up to 42 days of dosing Primary outcome: 59% of eltrombopag patients achieved primary endpoint (platelet count >50,000/μL), with median platelet counts of 18,000/μL (placebo) and 69,000/μL (eltrombopag).
Psaila et al. ASH 2007: abs 1301	III	Substudy of larger treatment studies, where adult patients with chronic ITP received eltrombopag	17	Primary measure: platelet count, mean platelet volume and the immature platelet fraction (or reticulated platelet count) Primary outcomes: 11/17 patients responded to eltrombopag with a rise in platelet count of >30 × 10^9/L. MOA of eltrombopag causes release of new platelets into circulation; direct binding to c-Mpl receptors on platelets
Cheng et al. ASH 2008: abs 4000	Ib	A 6-month, randomized, double-blind, placebo-controlled, Phase III study that evaluated the efficacy and safety of eltrombopag in previously treated adults with chronic ITP with platelet counts <30,000/μL	197	Primary measure: The primary endpoint was the odds of responding (platelets 50,000 to 400,000/μL) during the treatment period for patients receiving eltrombopag relative to placebo. Bleeding symptoms were evaluated using the WHO Bleeding Scale Primary outcome: patients who received eltrombopag were 8 times more likely to achieve platelet counts 50,000 to 400,000/μL during the 6-month treatment period compared with patients on placebo (OR [95% CI] = 8.2 [4.32, 15.38]; *P*<0.001). Significantly fewer patients treated with

				eltrombopag had any bleeding (WHO Grades 1-4; *P* <0.001) or clinically significant bleeding (WHO Grades 2-4; *P* <0.001) throughout the trial compared with patients treated with placebo. A higher incidence of hepatobiliary laboratory abnormalities were reported in the eltrombopag group (13%) compared with the placebo group (7%)
Bussel et al. ASH 2007:abs 566	IIa	EXTEND, an open-label extension study designed to assess the long-term safety and efficacy of oral eltrombopag	61	Primary measure: safety and efficacy of eltrombopag in open-label extension study Primary outcome: EXTEND study suggests that eltrombopag is well tolerated and sustains increased platelets counts during long-term treatment

Colchicine

Citation	LOE	Study design	Patient numbers	Summary
Narang et al. *Am J Haematol* 2003;74:263–267	III	Case study: series of case studies treated with rituximab (6 in total)	6	In 1 case, patients received multiple therapies to manage ITP including a brief therapeutic trial with colchicine, which was ineffective (before patient received an effective regimen with rituximab)
Serpa et al. *J Thromb Haemost* 2007;5:abs P-W-312	III	Case study of ITP patient treated with rituximab	1	Vincristine, colchicine and danazol were included in this patient's treatment regimen without good results

PBST

Citation	LOE	Study design	Patient numbers	Summary
Zaydan et al. *Bone Marrow Transplant* 2002;29:87–89	III	Case study of peripheral blood progenitor transpant (PBPT) in ITP patient. 19-year-old male with long history of ITP; diagnosed at 5 yrs	1	Primary outcome: resolution of chronic refractory ITP with syngeneic PBPT. Platelet counts at 6 and 11 months post-transplant were 374,000 and 373,000, respectively
Butler et al. *Bone Marrow Transplant* 2003;31:621–622	III	Case study of ITP patient; 56-year-old female with chronic, refractory AITP	1	Primary outcome: successful remission of chronic, refractory AITP following non-myeloablative allogeneic stem cell transplantation

Elli et al. *Haematologica* 2007;92:e7–8	III	Case study of AITP patient; 60-year-old female	1	Primary measure: myelo- and immunosuppressive chemotherapy followed by autologous peripheral blood stem cell (PBSC) transplantation for severe chronic refractory AITP Primary outcome: Resolution of chronic refractory ITP with T-cell depleted autologous PBSC transplantation. However, deeper studies and prolonged follow-up need to demonstrate the percentage and durability of the remission and to determine the risk/benefit profile
Passweg et al. *Autoimmunity* 2008;iFirst:1–6	IIb/III	Summary of data on hematopoietic stem cell transplantation (HSCT) to treat severe, refractory, haematologic autoimmune cytopenia, including several case reports, a phase II study reported by researches at the NIH, and a report on outcome of patients reported to the European Group of Blood and Marrow Transplantation (EBMT) autoimmune disease registry		Primary outcome: Autologous and allogeneic HSCT may induce response in a considerable proportion of patients with autoimmune cytopenia of long duration

Plasmapheresis

Citation	LOE	Study design	Patient numbers	Summary
Masseau et al. *Rev Med Interne* 2005;26:824–826	III	Case study of 2 acute refractory ITP patients	2	Primary outcome: plasmapheresis normalised the platelet count of two patients with severe acute ITP. Plasmapheresis may warrant more research as an emergency treatment in this setting

Supportive care – inhibition of menstrual bleeding

Citation	LOE	Study design	Patient numbers	Summary
Lete et al. *Eur J Contracept Reprod Health Care* 2008;13(3):231–237.	IIb	Prospective-observational study to evaluate patient satisfaction and improvement in quality of life (QoL) among women with idiopathic menorrhagia treated with the levonorgestrel intrauterine system (LNG-	255	Primary measure: one-year follow-up of women who had a LNG-IUS inserted for control of idiopathic menorrhagia; bleeding, tolerability, user satisfaction, and health-related QoL (SF-36 questionnaire) were assessed

		IUS)		Primary outcome: statistically significant reduction in the amount of bleeding, an increase of haemoglobin and ferritin levels, and an improved QoL score – a high degree of satisfaction was reported by >98% of patients

Combination chemotherapy

Citation	LOE	Study design	Patient numbers	Summary
Tao et al. *Chin Med J* 2007;120:1643–1646	IIb	Retrospective; Chronic ITP patients refractory to splenectomy treated with combined chemotherapy. Patients received following combinations: CAOP (cyclophosphamide/azathioprine/ vincristine/prednisone) COP (cyclophosphamide/vincristine/ prednisone) COE (cyclophosphamide/vincristine/ etoposide) COEP (cyclophosphamide/vincristine/ etoposide/prednisone) CHAOP (cyclophosphamide/ homoharringtonine/azathioprine/vincristine/ prednisone) CHOP (cyclophosphamide/ homoharringtonine/vincristine/prednisone) VAEP(vincristine/azathioprine/etoposide/ prednisone) CHAP (cyclophosphamide/ homoharringtonine/azathioprine/ prednisone)	31	Primary measure: CR – a platelet count over 100×10^9/L persisting for at least 2 months on no maintainence therapy, PR – platelet count within 50×10^9/L – 100×10^9/L, NR, platelet count below 50×10^9/L Primary outcome: overall response rate was 67.9% and chemotherapy was well tolerated. Longer follow-up study required

Quality of life in patients failing first- and second-line therapies

Citation	LOE	Study design	Patient numbers	Summary
Snyder et al. *Curr*	IV	Cross-sectional, descriptive study	2033	Primary measure: ITP patients –SF-36, EQ-5D,

Med Res Opin 2008;24(10):2767–2776		assessing the health-related quality of life (HRQOL) of ITP patients compared with age and gender matched controls		and ITP-Patient Assessment Questionnaires (ITP-PAQ); controls –SF-36 and EQ-5D. SF-36 and EQ-5D scores were compared; associations between splenectomy status, duration of illness, and platelet count with ITP patients' HRQOL scores were also examined. Primary outcome: ITP patients scored worse on seven of eight SF-36 domains and the Physical and Mental Summary scores (all $p < 0.05$) and on the EQ-5D visual analog scale (65.5 vs. 82.3; p¼0.002). Splenectomised ITP patients had similar SF-36 and EQ-5D scores to non-splenectomy patients but scored significantly worse on 5 of 10 ITP-PAQ scales (all $p < 0.05$). ITP patients diagnosed <5 years had worse Bother and Overall QoL scores than less recently diagnosed patients. Lower platelet count was consistently associated with worse ITP-PAQ scores and had weaker associations with SF-36 and EQ-5D scores.
McMillan et al. *Am J Hematol* 2008;83:150–154	IV	Evaluation of the health-related quality of life (HRQOL) of adult ITP patients compared with the general US population and patients with six other relatively common chronic disorders	73	Primary measure: HRQOL was assessed with the Short-Form 36 (SF-36) questionnaire Primary outcome: HRQOL scores in patients with ITP were lower than those of the US general population for all eight domains and for both summary scores (statistically significant in every case except Mental Health). Patients with ITP had significantly lower physical component scores (PCSs) than did patients who indicated that a physician had informed them that they had hypertension ($P<0.0001$), arthritis ($P=0.0014$), or cancer ($P=0.0003$). Scores from diabetic and ITP patients were nearly identical ($P=0.52$), whereas patients with CHF or a missing or paralyzed limb scored significantly lower than patients with ITP ($P=0.002$ and $P=0.0226$, respectively).