Secondary treatments for paediatric patients with persistent/chronic primary ITP at a specialised haematology clinic in Durban, South Africa

By

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As the candidate's supervisor I have approved this thesis for submission.

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Overview of the thesis

The variance in standard treatment guidelines for patients with persistent/chronic immune thrombocytopenia (ITP) makes the sequential selection of secondary therapies challenging. Benefits and risks associated with use of different combinations of therapies for persistent/chronic immune ITP need evaluation.

The aim of this study was to describe the response rates and adverse effects of secondary therapies utilised in the management of patients with persistent/chronic ITP at a specialised haematology clinic at a quaternary hospital in Durban, South Africa.

This retrospective, observational, descriptive study reviewed records of secondary treatments utilised for children with persistent/chronic primary ITP from the haematology clinic at Inkosi Albert Luthuli Central Hospital between 2010 and 2020. We extracted data from the electronic based registry using the Meditech filing system at the institution. Patients' demographics, presenting clinical features, laboratory data (full blood counts, viral and autoimmune screens, HIV status, bone marrow findings) and therapeutic interventions were recorded. Outcome variables included platelet responses, the number of bleeding episodes during follow up and adverse therapeutic effects at 6, 12 months post diagnosis and at last follow up.

Management of persistent/chronic primary ITP is difficult with patients responding to a combination of therapies. Whilst international guidelines help to stratify the sequence of use of secondary therapies in high-resource settings, they are not applicable in low-resource settings where access to thrombopoietin-receptor agonists and rituximab is limited. Sequential selection of secondary therapies remains a challenge in providing care in these settings. We hoped that this study would highlight benefits and risks associated with different combinations of therapies accessible to low-resource settings.

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Abbreviations & definitions

Abbreviations

Immune Thrombocytopenia	ITP
Systemic lupus erythematosus	SLE
Human immunodeficiency virus	HIV
Thrombopoietin receptor antagonists	TPO-RAs
Low middle income countries	LMICs
ITP International Working Group	ITP-IWG
International Consensus Report	ICR
American Society of Haematology	ASH
British Society of Haematology	BSH
World Health Organization	WHO
Health-related quality of life	HRQoL
Intravenous immunoglobulin	IVIG
Intravenously	IV
Mycophenolate mofetil	MMF
Food and Drug Administration	FDA
Bone marrow aspirate and trephine	BMAT
Azathioprine	AZA

Definitions

Platelet response:

Complete response - An improvement of the platelet count to more than 100 $x10^9$/L.

Partial response - A platelet count between 30-100 x 10^9/L.

No response - Any platelet count less than 30 x 10^9/L.

Classification of bleeds according World Health Organisation:

Grade 1-Minor blood loss, not requiring red cell transfusion e.g. petechial bleeding on <2 dependent sites, Oropharyngeal bleeding, Epistaxis <30 minutes.

Grade 2-Clinically significant blood loss, not requiring red cell transfusion e.g. profuse epistaxis or oropharyngeal bleeding (>30 minutes), multiple bruises >2 cm or any bruise>10 cm, macroscopic haematuria.

Grade 3-Clinically significant blood loss not associated with haemodynamic instability but required red-cell transfusion.

Grade 4- Debilitating blood loss associated with haemodynamic instability, including retinal and cerebral haemorrhage.

Remission - A platelet count more than 100 $x10^9$/L and absence of bleeding episodes.

Relapse – A platelet count that at some point improved to more than 100x 10^9/L but subsequently reduced to count less than 100 x 10^9/L or any rebound bleeding episodes at the last recorded visit.

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CHAPTER 1: LITERATURE REVIEW

Introduction

Immune thrombocytopenia (ITP) is a rare, acquired autoimmune condition characterized by a low platelet count (<100 x10^9/L) and an increased risk of bleeding. The bleeding could be minor, major or life threatening. The risk of bleeding increases with a lower platelet count and is highest when the platelet count drops below 10 x 10^9/L. Primary ITP is a diagnosis of exclusion, where the secondary causes of ITP, such as common viral infections and autoimmune conditions (e.g., Evans syndrome, systemic lupus erythematosus), have been excluded. In 2007, the International Working Group of experts from several European haematological societies held a conference in Italy where they redefined primary immune thrombocytopenia as an isolated thrombocytopenia (peripheral blood platelets < 100 x 10^9/L) in the absence of other causes of thrombocytopenia. They further reclassified phases of ITP into "newly diagnosed ITP" (within three months from diagnosis), "persistent ITP" (3-12 months from diagnosis), and "chronic ITP" (lasting for more than 12 months from diagnosis)[1].

Epidemiology

In children and adolescents, the annual incidence rate of ITP is 2–7 new cases per 100,000 with a prevalence 4–5 per 100,000[2, 3]. It is the commonest acquired cause of low platelet count in childhood with a peak age incidence of 1-5 years (range 2-10 years) and the mean age of presentation being 5.7 years[3]. Boys are more commonly affected than girls, especially in infancy and early childhood[2]. A significant gender disparity is observed in adolescent and adult primary ITP, with a female-to-male ratio of approximately 2:1[4-6]. This is generally thought to be related to the increased immune activity in adult females thus predisposing them to autoimmune disorders[7, 8]. In contrast to primary ITP, secondary ITP does not exhibit a female predominance[9]. Overall, less than 25% of affected children have persistent and chronic ITP[10].

Pathophysiology

The pathogenesis of ITP is complex, affecting multiple components of the immune system and causing both peripheral destruction of platelets and impaired central megakaryopoiesis and platelet production in the bone marrow[11]. Various mechanisms have been described in the literature i.e., anti-platelet antibody-mediated clearance, abnormalities in cell-mediated immunity, and suboptimal thrombopoietin response [2, 12].

The pathophysiology of thrombocytopenia in ITP is immune-mediated and must be distinguished from either decreased platelet production e.g., aplastic anaemia, increased platelet consumption e.g., disseminated intravascular coagulation) or increased platelet sequestration e.g., hypersplenism, infections etc.

A critical analysis of the full blood count and peripheral smear is crucial for correct diagnosis. Abnormal low platelet count on peripheral smears must be separated from large sized platelets indicating true hereditary thrombocytopenia or clumps of platelets indicating infections e.g., tuberculosis. An observational study of children on the Paediatric and Adult Registry on Chronic ITP (PARC-ITP) between 2004 and 2017 with 24 months follow-up, reported 99 out of 3581 (2.8%) children with initial diagnosis of primary ITP, having secondary ITP. Infectious and autoimmune diseases were the main causes for secondary ITP reported in 43 (1.2%) and 38 (1.06%) patients, respectively. Other underlying causes were malignancy (0.17%), aplastic anaemia (0.2%), immunodeficiency (0.2%) and drugs (0.03%)[13].

Clinical features and investigations

ITP typically presents with clinical manifestations such as wet purpura, petechiae, bruising, and epistaxis, and may also be incidentally diagnosed in asymptomatic individuals with isolated thrombocytopenia.

A full blood count with a smear is mandatory in all cases. Tests for autoimmune diseases and common viral infections including human immunodeficiency virus, cytomegalovirus, herpes simplex virus, varicella, parvovirus etc. are required. A bone marrow aspirate and trephine (BMAT) is performed for all cases of persistent/chronic ITP but not indicated in newly diagnosed ITP.

Management

Over the years, ITP has seen expansive changes in its treatment strategies.

Newly diagnosed ITP

In most children, acute or newly diagnosed ITP disease resolves within a few weeks to months[14]. Management includes observation for asymptomatic or mildly symptomatic children, corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin[14-17].

- Cautious observation

The majority of children with newly diagnosed ITP are asymptomatic or develop only mild bleeding symptoms[15]. A comparative prospective observational study of children and adults with immune thrombocytopenia on the PARC-ITP registry concluded that children are much more likely than adults to experience spontaneous disease remission, with up to 70% of paediatric patients resolving by six months[4]. This

study was limited by diverse data sources from different countries, voluntary registration, and significant loss to follow-up, but a local single-centre study at Tygerberg Hospital similarly found that South African children present like those in other settings, with observation alone being a successful treatment modality[18]. This was further reinforced by a retrospective study done at Red Cross Memorial War Children's Hospital in Cape Town, where authors reported no statistical difference in time to resolution between those patients that had "no treatment" as compared to those who received treatment[19]. Given the low risk of severe bleeding, the likelihood of spontaneous remission, and substantial side effects of ITP therapies, first-line management for paediatric ITP is often careful observation[15].

- Corticosteroids

There are various mechanisms of action for corticosteroids in the treatment of ITP. They inhibit phagocytosis and antibody synthesis, improve platelet production, and increase stability of microvasculature thereby decreasing platelet consumption[20]. Corticosteroids are recommended as first line therapy over intravenous immunoglobulin or anti-D immunoglobulin due to their low cost, universal availability, ease of outpatient administration, no exposure to multiple blood donors and overall minimal adverse effects [14, 16, 17]. Prednisone 2-4mg/kg, 12 hourly for seven days or dexamethasone 0.6 mg/kg, 6 hourly for four days for non-life-threatening bleeds are recommended. Use is limited by adverse effects, particularly if prolonged administration is required[14].

- IVIG

IVIG downregulates Fc mediated phagocytosis of antibody-coated platelets. The high cost of IVIG has necessitated cautious use in resource-constrained settings, where prednisone is often favored as a more cost-effective treatment alternative[19]. It is often used when rapid platelet count elevation is necessary, such as in cases of significant bleeding or before surgery[16]. The standard treatment dose of IVIG is 2g/kg, administered over a 48-hour period.

- Intravenous Anti-D immunoglobulin

Anti-D immunoglobulin, licensed by the Food and Drug Administration (FDA) as treatment of ITP in Rh-positive, non-splenectomized children in 1995, works by inducing mild hemolysis, thereby diverting autoantibodies away from platelets.

Persistent/chronic ITP

Patients with persistent (no response after three months of first line therapy) or chronic ITP (no response at 12 months of therapy) require secondary therapies. There is a paucity of published literature with respect to optimal sequence of selection of secondary therapeutic modalities. These have evolved over time and continue to expand. Options include corticosteroids, immunosuppressants like azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), ciclosporin A and rituximab, thrombopoietin-receptor agonists, and splenectomy. Recommendation for the use of available therapies vary internationally but also depends on availability of treatment options.

The aim of this thesis is to describe the response rates and adverse effects of secondary therapies utilised in the management of patients with persistent/chronic ITP. We searched published literature using PubMed and Google Scholar initially in September 2020 and again in September 2024. The terms of search included: chronic and persistent ITP, treatment response, splenectomy, corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), thrombopoietin receptor agonists (TPO-RAs), ciclosporin A and rituximab.

A. Corticosteroids

Whilst corticosteroids are the backbone of first-line therapy for ITP, the treatment guidelines have consistently advised against their use in patients with persistent or chronic ITP as prolonged exposure at moderate to high doses is associated with substantial adverse effects[14, 17, 20, 21]. These documented side effects include weight gain, mood changes, sleep disturbance, gastritis, gastrointestinal bleeding, hypertension, hyperglycemia, and when used chronically, cataracts and osteoporosis. The International Consensus Report (ICR) highlighted that over time, these detrimental effects of corticosteroids far outweigh their benefits [14]. The ASH guidelines and the ICR do not recommend prolonged courses of corticosteroids[14, 17]. Both expert panels urge brief treatment durations of corticosteroids, as well as other second-line options such as thrombopoietin-receptor agonists, rituximab, and splenectomy for the treatment of ITP beyond first line [14, 17]. Despite these guidelines, corticosteroids remain the most commonly used treatment for all phases of ITP in numerous countries, including high-income nations such as the United States and Spain[22-24].

Some researchers believe that corticosteroids still have a role in the management of persistent and chronic ITP. In 2010, Dinesh et al. conducted a study in India to assess the efficacy of short-course high-dose dexamethasone in children with chronic ITP. Notably, the authors' definition of treatment response differed slightly from the widely-accepted international guidelines and our current study. Treatment response was categorised as follows: a complete response was defined as a platelet count of 150 $x10^9$/L or higher, a moderate response as a platelet

count of 50-150 x10^9/L, a minimal response as a platelet count of 20-50x10^9/L, and no response when a platelet count remained below 20x10^9/L. Thirteen patients with chronic ITP were given high-dose dexamethasone (20 mg/m^2 intravenously (IV) daily for four days, for four cycles, repeated every 15 days) for ten months[25]. Of the 12 patients evaluated, there was a complete response in eight (66.6%), moderate response in two (17%) and no response in two (17%) patients with a median relapse-free duration of five months observed. They concluded that short-course high-dose dexamethasone was a safe and effective therapy in chronic ITP.

B. Azathioprine

Although azathioprine has been widely used to treat ITP for decades, there is no original research data on its efficacy in improving bleeding, or its effects on health-related quality of life (HRQoL), and fatigue[21]. The 2019 ASH guidelines did not make any recommendations on azathioprine due to lack of data[17]. The ICR also raised concerns about lack of data in populations of all ages, but it recommends that azathioprine can still be used as an add on to thrombopoietin receptor agonist[14]. It may be presumed safer and possibly equally effective as other better-studied therapies, but use of azathioprine is more challenging in the absence of data.

C. Mycophenolate mofetil

Mycophenolate mofetil (MMF), an immunosuppressant has a direct inhibitory effect on T-cells. It is widely used, as a second-line agent in persistent/chronic ITP at the recommended dose is 20-40 mg/kg /day. Overall response rate can reach up to 50-60%, with a time to response ranging between four and six weeks[26]. Data on use of MMF for paediatric ITP is sparse. In the largest reported cohort of 30 children with primary ITP (newly diagnosed, persistent, or chronic), treatment with MMF achieved a response rate of 56%, and 29% of patients relapsed[27]. Mild side effects such as gastrointestinal disturbances and generalized body weakness were observed in some patients. A more recent single-centre study reported a 73% response rate when treating clinicians used titrated doses of up to 2400 mg/m^2/d in 16 paediatric patients with chronic ITP[28]. These doses were well tolerated with mild adverse effects.

The ASH 2019 guidelines and the ICR did not prioritize a review of MMF due to limited availability of data, a lack of direct comparisons, and large variability in outcome measures[14, 17]. Although the British Society of Haematology (BSH) does not recommend routine use of MMF, these experts did highlight the need for further evaluation of MMF with prospective studies as it has been extensively used in other paediatric autoimmune conditions with good safety profile[3].

D. Cyclophosphamide

Cyclophosphamide, a cytotoxic drug has been used an immunosuppressive agent to treat autoimmune disorders at low doses. Due to limited data and the potential for serious long-term sequelae, including malignancy and infertility, its use in paediatric ITP is increasingly discouraged[29].

E. Ciclosporin A

Ciclosporin A is a calcineurin-inhibitor that has been widely used in patients with autoimmune disorders including ITP. Though there is paucity of data, some studies have reported success with its use in paediatric chronic ITP.In a meta-analysis of seven randomized controlled clinical trials from Asia, ciclosporin demonstrated efficacy and safety as second-line treatment for ITP in adults and children, typically as part of combination therapy[30].

F. Rituximab

Rituximab is an anti-CD-20 monoclonal antibody, used in a wide variety of autoimmune conditions including ITP. It causes a rapid depletion of CD-20-positive B cells which are responsible for antibody production, a decrease in serum immunoglobulin levels, and an increased number of T-regulatory cells[21]. It depletes short-lived plasma cells but does not affect long-lived plasma cells. Effects of rituximab last for about six to twelve months. There is over a 25% chance of relapse.

Rituximab has not been licensed for the treatment of ITP; however, studies report responses in children with chronic ITP[14]. In a study of 66 children with ITP treated with rituximab, 57% had an initial response but responses waned over time with durable remission rates of 21% to 26% at five years[31]. Whilst the ICR recommends that rituximab be used for chronic ITP, ASH updated guidelines suggest that it be used as a “splenectomy sparing drug”, but not prior to thrombopoietin receptor agonists[14, 17]. There is increasing concern about adverse effects such as persistent hypogammaglobulinemia and potential for haematological malignancies[17, 32]. The BSH does not recommend use of rituximab in paediatrics due to toxicity to the immature immune system[3].

Rituximab does not seem to improve health-related quality of life in patients with ITP. A randomized trial using the Short Form 36 Health Survey Questionnaire found that rituximab had no impact on the physical or mental

quality of life compared with placebo[33]. Furthermore, 22% of patients who received rituximab reported fatigue compared with 8% of patients who received placebo.

G. Thrombopoietin receptor agonists

Thrombopoietin receptor agonists (TPO-RAs) bind to and stimulate the thrombopoietin receptor to increase platelet production, but these agents are not considered curative [21]. Eltrombopag and romiplostim have been studied extensively in children.

Randomised trials in children and adults have demonstrated an initial platelet response of 59% to 75%, with eltrombopag and a durable response of 62% with continued treatment in chronic ITP[34]. The PETIT 1 and PETIT2 studies of eltrombopag in children with chronic ITP reported a platelet count of more than 50 at least once; in 80% of patients; in PETIT2, 40% of patients had a platelet count of more than 50 for more than six weeks without rescue (defined as a composite of new ITP medication or platelet transfusion). Several case series after eltrombopag report patients with remission [21].

An analysis of five eltrombopag trials reported a decrease from baseline in bleeding of around 50% to 73% for eltrombopag-treated patients overall and a decrease in bleeding from baseline around 26% to 39% by week two. This trend was maintained throughout the study period [35]. No cases of World Health Organisation (WHO) Grade 3 or 4 bleeding, defined as clinically significant blood loss requiring blood transfusion, or debilitating blood loss including retinal and cerebral haemorrhage, respectively, were reported in patients treated with eltrombopag in the PETIT trials [36].

In PETIT1, children receiving eltrombopag had a small improvement in the Kids' ITP Tool score but did not meet criteria for the minimal important difference [35]. Thus, the effect of eltrombopag on health-related quality of life in children with ITP is not clear.

The FDA, as well as the European Medicines Agency, have licensed eltrombopag for use in children older than one year with chronic ITP. Whilst both the ICR and the ASH updated guidelines recommend use of TPO-RAs as second-line therapy, these agents are extremely costly and not readily available in all countries.

Adverse effects like bone marrow reticulin formation (around 2%), thrombotic events (around 4%), hepatotoxicity and cataract formation are major concerns for treating clinicians [37].

H. Splenectomy

The spleen is the primary site of platelet destruction. It is an important organ for B-cell development and diversification of the T-cell repertoire. Splenectomy thus removes the mechanism of platelet destruction as well as a large source of antibodies in patients with ITP[20]. It is an effective therapeutic option for chronic ITP with high and durable response rates [21].

The splenectomy registry of the Intercontinental Cooperative ITP Study Group collected the splenectomy data of paediatric patients with ITP between June 1997 and September 2017 with the aim of analyzing long-term outcomes of children with primary ITP. The overall response rate was 93% with 81% showed complete response. Of the complete responders, 76% showed a sustained complete response and 24% showed fluctuation of platelet counts to $<100\times10^9$/L [38].

Splenectomy is, however, associated with a lifelong risk for life-threatening bacterial sepsis, historically at a rate of 0.73 per 1000 patient-years [21]. Whilst it is the only method that can change the course of the disease, the postoperative risk of infection is a deterrent to its routine use[14]. Other concerning short-term complications of splenectomy include bleeding, local infection, and thrombosis.

The variance of opinions about the role and timing of splenectomy in management of paediatric ITP thus remains. The ITP international working group (ITP-IWG) recommends that splenectomy only be considered in children who have failed all medical therapies and after 12 to 24 months from diagnosis, as there is the possibility of response to treatment over time[14]. Similarly, the BSH suggests that splenectomy still has a role in the management of paediatric chronic ITP; whilst the 2019 ASH guidelines recommended that it be avoided in the paediatric population[3, 17, 39].

Owing to the development of new therapeutic options, splenectomy is rarely performed in high-income countries currently [1, 16]. However, it remains an important treatment option in low middle-income countries[18, 19, 40].

Impact and Outcome of ITP

Platelets are an essential component of vascular integrity. Thrombocytopenia or impaired quality and functioning of platelets increases the risk of bleeding[3]. Depending on the site, frequency, and extent of bleeding, this can have a significant impact on health. Although many children with ITP may have a low, risk of bleeding, thrombocytopenia can impact the quality of life of such patients, including parental anxiety, social isolation, sporting restrictions, and compromised school attendance. Although life expectancy has been previously reported to be significantly low in adult studies[41], ITP-related mortality is almost 0% in recent paediatric studies[2].

Conclusion

The American, British, and European guidelines on paediatric persistent/chronic ITP are based on retrospective and indirect comparisons due to paucity of prospective clinical trial data from direct comparisons of second-line therapeutic options. Whilst these international guidelines help to stratify the sequence of use of secondary therapies in high-resource settings, they are not applicable in low-resource settings where access to thrombopoietin-receptor agonists and rituximab is limited due to cost. Sequential selection of secondary therapies remains a challenge in providing care in these settings. Benefits and risks associated with different combinations of therapies accessible to LMICs need evaluation.

Aim of study

To describe the outcomes of children with primary ITP who developed persistent/chronic ITP treated in a haematology clinic at a quaternary hospital in Durban, South Africa over a decade: 2010 to 2020.

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CHAPTER 2: SUBMISSION READY MANUSCRIPT

Secondary treatments for paediatric patients with persistent/chronic primary ITP at a specialised haematology clinic in Durban, South Africa

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Abstract

Background: Variance in standard treatment guidelines for patients with persistent/chronic immune thrombocytopenia (ITP) makes the sequential selection of secondary therapies challenging. Benefits and risks associated with use of different combinations of therapies needs evaluation.

Methods: This retrospective, observational, descriptive study reviewed records of secondary treatments utilised for children with persistent/chronic primary ITP from the haematology clinic at Inkosi Albert Luthuli Central Hospital between 2010 and 2020. We extracted data from the electronic based registry using the Meditech filing system. We captured patients' demographics, presenting clinical features, laboratory data, and therapeutic interventions. Outcome variables included platelet responses, number of bleeding episodes, and adverse effects at 6, 12 months post therapy and at last follow up.

Results: Of the 30 patients enrolled, fourteen (46.7%) received immunosuppressive agents alone (azathioprine, rituximab, ciclosporin, and prednisone) and 16 (53.3%) had splenectomy in addition to immunosuppressive agents. Nine of the 14 children (64.4%) treated with immunosuppressive therapy alone achieved remission, while seven of the 16 children (43.8%) who underwent splenectomy achieved remission. Eleven of the 16 patients (68.8%) had a complete response by 12 months of diagnosis. Seven other patients (23.3%) responded initially but relapsed during the 2- to 10-year follow up. Children who had immunosuppressive therapy and splenectomy had similar rates of adverse effects as those who had immunosuppressive therapy alone ($p>0.5$).

Conclusion: Selection of secondary therapies for non-acute primary ITP remains difficult with patients responding to various combination of therapies and none showing clear advantages over others. Secondary therapies should be utilised on basis of availability, costs, social circumstances, and medicine safety.

Introduction

Primary Immune thrombocytopenia (ITP), an isolated immune-mediated peripheral blood platelets count of < 100 x 10^9/L, is a diagnosis by exclusion of known secondary causes of thrombocytopenia. It is the commonest acquired cause of low platelet count in childhood, affecting 4–8 per 100 000 children each year.[1, 2]. The degree of thrombocytopenia determines the risk of bleeding. The impact of bleeding depends on its site, frequency, and extent. In addition, the condition affects the quality of life of sufferers viz. loss of socialising, decreased sports activity and time lost from school from clinic and emergency hospital visits[3]. The majority of cases of primary newly diagnosed ITP recovers spontaneously or with corticosteroids within 3 months of onset of disease[4, 5]. Approximately 25% of affected children however develop persistent (3-12 months) or chronic (beyond 12 months of presentation) disease[4]. Children with persistent/chronic ITP require secondary therapies including immunosuppressants (such as corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil, ciclosporin A, and rituximab), thrombopoietin-receptor agonists (TPO-RAs), and splenectomy[1, 6-8]. The optimal sequence for selection of these therapies remains unclear. Studies comparing the benefit and risks of these treatment options are scarce, while outcome measures are inconsistent. Despite the establishment of standard guidelines for both diagnosis and response to therapy, recommendations for use vary internationally, and are based on efficacy, safety, cost, and practical applicability [6, 7, 9].

The prolonged use of corticosteroids for persistent/chronic primary ITP is of concern due to serious adverse effects of Cushing's syndrome, hypertension, abnormal glycemic control, and infections[7, 9-11]. There is little data on the use of azathioprine in children but it's use in other autoimmune or oncological disorders has been associated with bone marrow toxicity[12]. The efficacy of rituximab in ITP for remission is around 60%[13], but half of these cases relapse and its use has been associated with adverse effects on the immature immune system including persistent hypogammaglobinemia[14-17]. TPO-RAs have shown a 70% success rate in children, achieving a sustained platelet response, and eliminating significant bleeding events that require red-cell transfusions or additional ITP treatments [6, 18-20]; however, the cost is exorbitant. Splenectomy with pre-surgery vaccinations is utilised more readily and earlier in children from Low-and Middle-Income Countries (LMICs) with persistent/chronic ITP even though the post-operative risk of infection is a concern. A review of paediatric splenectomy cases at two Johannesburg hospitals, Chris Hani Baragwanath and Charlotte Maxeke, found that the majority (39%) of splenectomies were performed for immune thrombocytopenia[21]. Antel et al. also concluded from their retrospective review of 73 patients who underwent splenectomy for ITP in Cape

Town that splenectomy remains the second-line treatment of choice, with newer treatments reserved for patients who are not surgical candidates[22].

The American Society of Haematology (ASH), the ITP International Working Group (ITP-IWG), and the British Society of Haematology (BSH) differ on recommendations on the role and timing of splenectomy and TPO-RAs [7, 9]. In children, use of TPO-RAs has been supported as first line therapy by the ASH and the BSH as it is associated with a reduction in bleeding frequency in the absence of adverse effects. In cases with no response to TPO-RAs or where there is relapse of the ITP, the ASH recommends switching to an alternate TPO-RAs with azathioprine or rituximab with corticosteroids for adolescent females[9]. The ITP-IWG does not support routine use of TPO-RAs due to lack of safety data in paediatrics. Splenectomy is recommended only in children who have failed medical therapies, 12 to 24 months from diagnosis[9] and should be avoided before 5 years of age. Direct efficacy and safety comparison from published data of individual treatments for persistent/chronic primary ITP is limited due to challenges with the lack of uniformed treatment endpoints[6]. The ITP-IWG recommends two primary outcomes: a "safe" platelet count, defined as any count that prevents major bleeding, and the absence of bleeding[8, 9].

The aim of this study was to describe the response rates and adverse effects of secondary therapies utilised in the management of patients with persistent/chronic ITP at a specialised haematology clinic at a quaternary health facility in Durban, South Africa.

Methodology

This was a retrospective, observational, descriptive study of children with persistent/chronic primary ITP, defined as an isolated thrombocytopenia (platelet count less than 100 x 10^9/L) with or without clinical history of mucocutaneous bleeding for longer than three months, who received secondary ITP therapies at Inkosi Albert Luthuli Central Hospital between 2010 and 2020. Patients with a secondary cause for the persistent/chronic ITP were excluded. Data was extracted from the electronic based registry using the Meditech filing system at the institution.

An Excel spreadsheet was used to capture patients' demographic data, presenting and ongoing clinical features, all laboratory data viz. full blood counts with differentials, viral and autoimmune screens, human immunodeficiency virus (HIV) status, bone marrow aspirate and trephine (BMAT) findings, pre-surgical ultrasound findings and vaccination history, and therapeutic interventions implemented over the study period. Outcome variables included platelet response at 6 months, 12 months, and last recorded visit; the number of bleeding episodes recorded at 0-6 months, 6-12 months and from 12 months until the last recorded visit; clinical

status at the last recorded institution visit up to the year 2020 and adverse clinical and laboratory effects for the duration of the study.

Ethics

Ethical approval was obtained from the University of KwaZulu Natal Biomedical Research Ethics Committee: Approval number: *BREC/0003807/22*. This study was retrospective in nature, therefore, informed consent/assent was not required.

Definitions

A "Complete platelet response" was an improvement of the platelet count to more than 100 $x10^9$/L. A "Partial response" was defined as a platelet count between 30-100 x 10^9/L. Any platelet count less than 30 x 10^9/L was regarded as "No response". Platelet responses were evaluated at the 6- and 12-month follow-up visits as well as at the last recorded follow up visit before 2021.

Bleeding episodes at initial presentation and during follow-up reviews were categorised as either major or minor, based on bleeding severity and the need for intervention. World Health Organisation (WHO) Grades 3 (clinically significant blood loss requiring red-cell transfusion) and 4 (debilitating blood loss associated with haemodynamic instability, including retinal and cerebral haemorrhage) were defined as major bleeds. All other bleeds that resulted in mild blood loss, not requiring red-cell transfusion, were regarded as minor (e.g., petechial bleeding, haematuria, haematoma, epistaxis, bruising). The number and severity of bleeding episodes were evaluated at 0-6 months, 6-12 months as well as between 12 months and the last recorded follow up visit.

Table 1: Classification of Bleeding Episodes

Category	Grade	Description	Examples
Minor bleeds	WHO Grade 1	Minor blood loss, not requiring red cell transfusion.	Petechial bleeding on <2 dependent sites, Oropharyngeal bleeding, Epistaxis <30 minutes
	WHO Grade 2	Clinically significant blood loss, not requiring red cell transfusion.	Profuse epistaxis or oropharyngeal bleeding (>30 minutes) Multiple bruises >2 cm or any bruise >10 cm, Macroscopic haematuria Musculoskeletal bleeding
Major bleeds	WHO Grade 3	Clinically significant blood loss not associated with haemodynamic instability but required red-cell transfusion.	
	WHO Grade 4	debilitating blood loss associated with haemodynamic instability, including retinal and cerebral haemorrhage.	

Complete response/remission was defined as a platelet count more than 100 $x10^9$/L with concurrent resolution of bleeding symptoms.

Relapse in disease was defined as a platelet count that at some point improved to more than 100x 10^9/L but subsequently reduced to count less than 100 x 10^9/L or any rebound bleeding episodes at the last recorded visit.

Statistical Evaluation

Descriptive statistics were used to summarize the data. Patients who received secondary therapies were classified into six different groups according to the type of secondary therapies received (figure 1). These groups were further classified into those who received combination immunosuppressive therapies with

splenectomy and those who received a combination of immunosuppressive therapy alone. Fisher's exact test was then used to compare categorical variables between the two groups. Numeric variables were normally distributed, and two sample t-tests used for numeric variables. Stata v17 was used for statistical analysis. The p-value of <0.05 was the threshold for statistical significance.

Results

A. Demographics and baseline characteristics

Thirty-six electronic files were identified with ITP at screening; six patients had secondary immune thrombocytopenia and were excluded from the analyses. Of the 30 patients included, fifteen were male, with a median age of 4.5 years (interquartile range [IQR] 2-8) at presentation. Twenty-three patients (76.7%) were of African descent whilst remainder were of Indian descent. All patients were HIV negative.

At diagnosis, 24 patients (80%) presented with minor bleeds; three patients (10%) presented with an incidental finding of thrombocytopenia while the remaining 10% of patients presented with major bleeds, including two with intracranial haemorrhage and one with blindness secondary to bilateral vitreous haemorrhage. The median platelet count at presentation was 7 x 10^9/L (IQR 3 – 12), with a median haemoglobin of 11.25 g/dl (IQR 10 – 11.7) and a median white cell count of 10.1 x 10^9/L (8.5 – 12.7). BMATs were performed on twenty-one patients (70%), and all results showed features consistent with ITP. Twenty-seven patients (90%) had an autoimmune screen performed and results were negative. None of the patients were screened for type 2B von Willebrand disease. All patients were confirmed as primary immune thrombocytopenia. Eleven patients (36.7%) had persistent ITP, while 19 patients (63.3%) progressed to develop chronic ITP. Unfortunately, only two out of sixteen patients who underwent splenectomy had ultrasounds to exclude polysplenia or splenuncles prior to surgery. However, no anatomical splenic abnormalities were detected intra-operatively.

B. Overall outcome measures (n=30)

At six months review, seventeen patients (56.7%) had a complete platelet response, seven (23.3%) had a partial platelet response, five (16.7%) had no platelet response and one child (3.3%) was lost to follow up. Eighteen (60%) had no bleeding episodes, eleven (36.7%) still had minor bleeds, whilst one (3.3%) was lost to follow up.

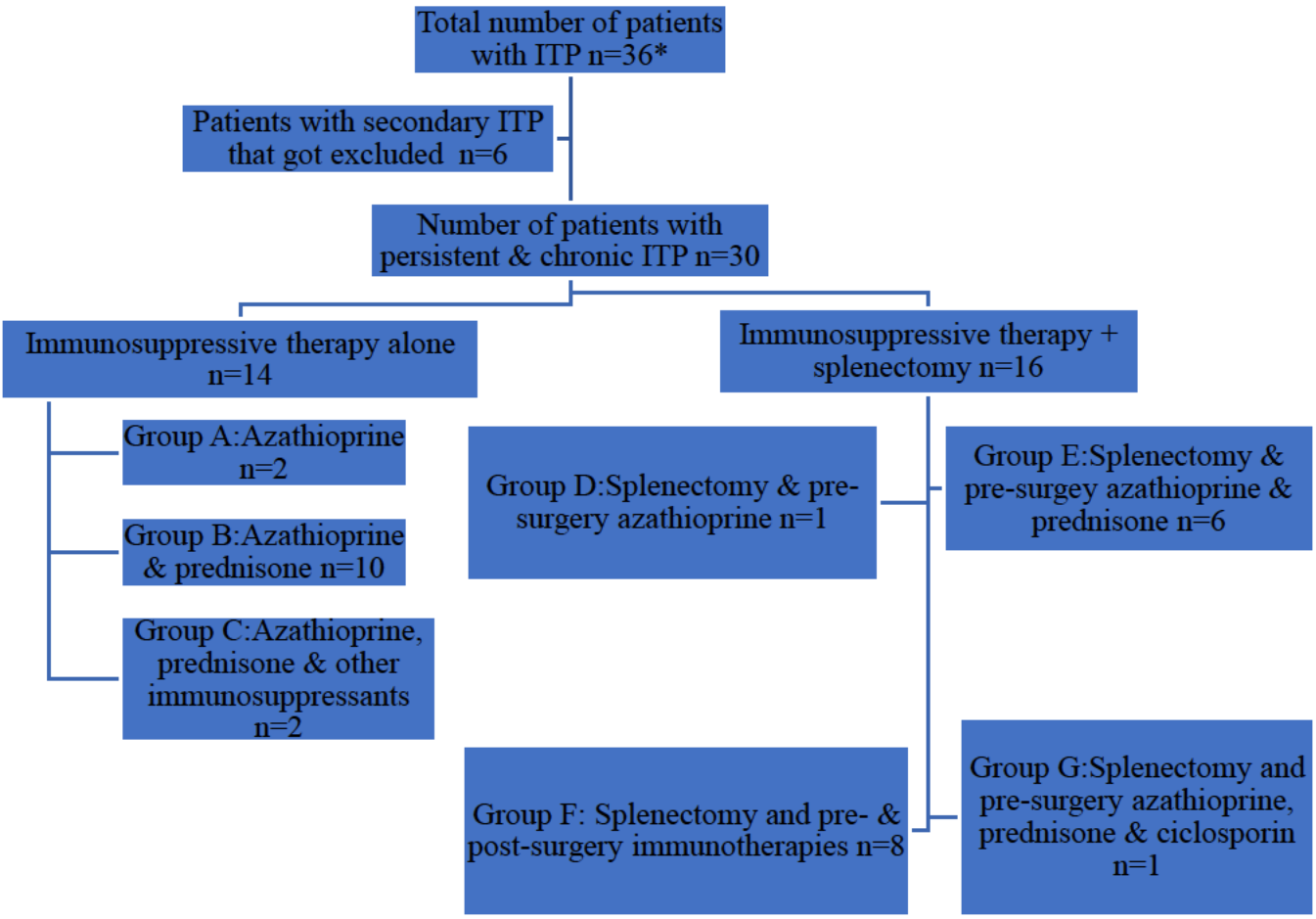
At 12 months review, eighteen (60.0%) had a complete platelet response, seven (23.3%) had a partial platelet response, four (13.3%) had no platelet response, and one (3.3%) was lost to follow up. Eighteen (60.0%) had no bleeding episodes, eleven (36.7%) still had minor bleeds, and one (3.3%) was lost to follow up.At last recorded

visit (range:2- to 10-years), sixteen patients (56.3%) were in complete remission, seven (23.3%) relapsed, two (6.7%) did not respond to therapy, and five (16.7%) were lost to follow up.

C. Description of the therapeutic interventions utilised and outcomes in children with persistent/chronic ITP (n=30)

Patients received variable treatments and they were characterized into groups A to G (**Figure 1**). Two patients received azathioprine alone (group A); ten patients received azathioprine and prednisone (group B); two patients received azathioprine, prednisone and rituximab or ciclosporin (group C); one patient had splenectomy and pre-surgery azathioprine (group D); six patients had splenectomy and pre-surgery azathioprine, and prednisone (group E); eight patients had splenectomy and pre and post-surgery immunotherapies viz.azathioprine, prednisone, rituximab, ciclosporin) (group F); whilst one patient had pre-surgery azathioprine, prednisone and ciclosporin and splenectomy (group G). All patients who underwent splenectomy received immunizations against *Streptococcus pneumoniae*, *Meningococcus*, and *Haemophilus influenzae* prior to surgery. They also received postoperative life-long penicillin v potassium (Pen VK) as per departmental protocol. There was no use of TPO-RAs.

Figure 1: Consort Diagram of Patients with Persistent/Chronic ITP from 2010-2020



* Only patients with persistent and chronic ITP are seen at the Paediatric Haematology Department at Inkosi Albert Luthuli Central Hospital.

Table *2*: Distribution of Treatment Groups Received by Patients with Persistent ITP vs Those with Chronic ITP

Persistent ITP n=11	Chronic ITP n=19
Group A: 2 patients Group B: 2 patients Group E: 6 patients Group F: 1 patient	Group B: 8 patients Group C: 2 patients Group D: 1 patient Group F: 7 patients Group G: 1 patient

D. Outcomes of persistent/chronic ITP cases related to therapeutic interventions administered (n=30)

Group A (n =2)

Both patients had a complete platelet response at six months review, but one still had minor bleeds. They were both in remission at 12 months review, and last recorded visit.

Group B (n =10)

At six months review, six patients had a complete platelet response but two of them still had minor bleeds. Three other patients had a partial platelet response whilst one patient had no response. Of the three patients that had partial response, two had minor bleeds.

At 12 months review, seven patients had a complete platelet response. However, one of these patients experienced a major WHO grade 4 upper gastrointestinal bleed, and four other patients had minor bleeds. Two other patients had a partial platelet response with no bleeds, whilst one patient still had no response.

Six patients were in remission at last recorded visit, three patients relapsed, and one was lost to follow-up.

Group C (n=2)

One patient had no response at 6- and 12-months reviews and was subsequently lost to follow up. The other patient had partial platelet responses at 6- and 12-months reviews and was in remission at the last recorded visit.

Group D (n=1)

This patient was in remission at 6- and 12-months reviews but subsequently got lost to follow-up.

Group E (n=6)

One patient had a partial platelet response and no bleeds at six months review. The other five patients were in remission.

All six patients were in remission at 12 months review and last recorded visit.

Group F (n=8)

At six months review, three patients had no response with minor bleeds, one patient had a partial response with minor bleeds whilst the other three patients were in remission. One patient was lost to follow up.

At 12 months review, two patients were in remission, two had no response with minor bleeds, and three patients had a partial platelet response. One patient had been lost to follow up. Of the three patients that had a partial platelet response, two had minor bleeds whilst one had no bleeds.

At last recorded visit, only one patient was in remission, three patients relapsed, two still had no response, and two patients were lost to follow up.

Group G (n=1)

This patient had a partial platelet response and no bleeds at six months review. This platelet response was sustained at 12 months, but this patient had minor bleeds.

At last recorded visit, there was no platelet response but there were no bleeding episodes.

E. Outcome of children on combined immunotherapy with and without splenectomy

Fourteen patients (46.7%) received a combination of medical immunosuppressive therapies alone (**Table 2**), with four (28.6%) of these patients having persistent ITP. Among the patients treated, eight out of 12 (66.7%) who received azathioprine alone or azathioprine with prednisone were in remission at their last recorded visit, while three (21.4%) relapsed, and one (7.14%) was lost to follow-up. One of the remaining two patients, who was on rituximab with other medical immunosuppressants, showed a partial platelet response at 6 and 12 months, and was in remission at the last recorded visit. The other patient, who received ciclosporin and other immunosuppressants, showed no response to treatment at 6 and 12 months and was subsequently lost to follow-up. Of the four patients with persistent ITP, two went into remission with azathioprine alone, while the other two achieved remissions with a combination of azathioprine and prednisone. Five patients (26.3%) with chronic ITP responded to immunosuppressive therapies alone, three relapsed or had no response to immunotherapies, two patients on the immunosuppressive therapy group were lost to follow-up.

Sixteen patients (53.3%) received combined immunosuppressive therapies (azathioprine, rituximab, ciclosporin, prednisone) and splenectomy. At the last recorded visit, seven (43.8%) were in remission at the last recorded. Additionally, nine (56.3%) patients had a complete platelet response and 11 (68.8%) were bleeding free at 12 months. Seven patients with persistent ITP underwent splenectomy, resulting in complete remission for all. Six patients received pre-surgical treatment with azathioprine and prednisone, while the seventh patient received

immunotherapies both before and after the splenectomy. Six patients with chronic ITP relapsed/had no response to a combination of splenectomy and immunosuppressants. Three other patients with chronic ITP got lost to follow up.

Some patients underwent splenectomy within 12 months of diagnosis. Notably, the complete response rate for persistent ITP was similar for those who had splenectomy (36.4%) and those who did not (36.8%).

F. Adverse Effects

Both patients on rituximab had abdominal pain while one patient also developed neutropenic sepsis requiring hospital admission. Children on immunotherapies with or without splenectomy had similar rates and types of serious adverse effects ($p>0.05$). The incidence of Cushing's syndrome, infections, blood dyscrasias (such as low total white cell count, neutropenia, and lymphopenia), hypertension, and gastrointestinal complications (including gastritis, haematemesis, and melaena stools) was similar in both groups (**Table 3**). In the splenectomy group, three patients (18.8%) developed thrombocytosis shortly after surgery, but this resolved by two years post-splenectomy in all patients. Despite pre-surgical vaccinations and life-long Pen VK, two patients (12.5%) were diagnosed with severe infections, one with complicated pyelonephritis and the other with neutropenic sepsis, however, microbiological cultures yielded no positive results. One patient suffered from recurrent tonsillitis; however, microbiological cultures were not performed to identify the underlying causative pathogen.

Table 3: Comparison of children who received immunosuppressive therapy alone vs those who had immunosuppressive and splenectomy (2010 -2020)

Characteristics			Immunosuppressive therapy and splenectomy (n=16)		Immunosuppressive therapy without splenectomy (n=14)		Total	p-value
Demographics	**Mean age (years) +/- SD at diagnosis**		5.1+/-2.59		4.93 +/-3.58			
			N	**%**	**n**	**%**		
	Sex	Male	5	33.3%	10	66.7%	15	0.07
		Female	11	73.3%	4	26.7%	15	
	Race	African	13	56.5%	10	43.5%	23	0.68
		Indian	3	42.9%	4	57.1%	7	
Presentation	**Major bleeds**		3	18.7%	0	0%	3	0.04
	Minor bleeds		13	81.3%	11	78.5%	24	
	Asymptomatic TCP	Yes	0	0%	3	100%	3	
		No	16	59.2%	11	40.7%	27	
	Blood results at diagnosis; mean & SD	Platelets	$10.63x10^9$/L	12.71	15.57	24.69		0.48
		Haemoglobin	9.94g/dL	2.61	11.1	1.81		0.18
		White cell count	$11.69x10^9$/L	4.64	9.88	3.22		0.23
Platelet response at 6 months		Complete	9	52.9%	8	47.1%	17	0.9
		Partial	3	42.9%	4	57.1%	7	
		No response	3	60%	2	40%	5	
		Lost to follow up	1	100%	0	0%	1	
Bleeding at 6 months		Yes	4	36.4%	7	63.6%	11	0.27
		No	11	61.1%	7	38.9%	18	
		Lost to follow up	1	100%	0	0%	1	
Platelet response at 12 months		Complete	9	50%	9	50%	18	0.7
		Partial	4	57.1%	3	42.9%	7	
		No response	2	50%	2	50%	4	
		Lost to follow up	1	100%	0	0%	1	
Bleeding at 12 months		Yes	4	36.4%	7	63.6%	11	0.2
		No	11	61.1%	7	38.9%	18	
		Lost to follow up	1	100%	0	0%	1	
Adverse drug reactions		Cushing's Syndrome	4	25%	5	35%	9	0.69
		Infections	3	18.8%	4	28.6%	7	0.67
		Thrombocytosis	3	18.8%	0	0%	3	0.23
		Blood dyscrasias	2	12.5%	6	42.9%	8	0.1
		Gastrointestinal complications	2	12.5%	2	14.2%	4	0.9
		Hypertension	3	18.8%	2	14.2%	5	0.9
Outcome at last follow up visit		Remission	7	43.8%	9	56.3%	16	0.16
		Relapse/ No response	6	66.7%	3	33.3%	9	
		Lost to follow up	3	60%	2	40%	5	

TCP = thrombocytopenia SD = Standard Deviation

DISCUSSION

The primary finding of this study was that just over half of children with persistent/chronic primary ITP had a complete response while a further 25% had an initial response and then relapsed during the follow up period of 2- to 10-years. The majority of patients (n=11, 68.8%) with a complete response had achieved this 12 months from diagnosis. Similar data was reported from the Paediatric and Adult Registry on chronic ITP, as well as the 10-year audit from Tygerberg Hospital, where 28% of paediatric patients with chronic ITP achieved remission within 24-26 months of diagnosis and 70% of patients had spontaneous remission within six months[23, 24], but is unlike a single-centre study by Jung et al which demonstrated an often benign course in children with 86% fully recovering within one year of diagnosis[25].

The bleeding outcomes observed in this study underscore the complexity of managing persistent and chronic ITP. Notably, 46.6% of treated patients continued to experience bleeding episodes in the first 12 months, although the majority of these events were minor. Only one patient required a red-cell transfusion following a major upper gastrointestinal bleed, highlighting the relatively low incidence of severe bleeding complications. These findings provide valuable insights into bleeding risks associated with persistent and chronic ITP, yet they do not offer clear guidance on the optimal management approach, leaving unanswered the question of whether patients should be treated aggressively or observed carefully with the hope of spontaneous remission.

This is particularly relevant in LMICs, where ongoing financial constraints, exacerbated by the lingering effects of the coronavirus pandemic, and a high burden of other diseases with worse outcomes, continue to pose significant challenges. Furthermore, access to expensive therapies remains limited in these settings.

In this study, two groups of children were treated for ITP. One group received immunotherapy alone, while the other group underwent splenectomy in addition to immunotherapy. Although the groups cannot be directly compared due the descriptive nature of the study, 64.4% of children receiving a combination of immunosuppressive therapy alone went into remission, with 50% having a complete platelet response at 12 months. In contrast, children who received both splenectomy and immunosuppressive therapies achieved a remission rate of 43.8%, with 56.3% having a complete platelet response at 12 months. Splenectomy was performed early in the treatment course of select patients. Notably, the remission rate for persistent ITP was comparable between patients who underwent splenectomy and those who did not. While splenectomy is the most predictable method for achieving a durable remission among patients with chronic ITP [6, 26], our study shows that the disease may persist beyond splenectomy in a quarter of patients. This finding is consistent with the remission rate of 66.7% previously reported at Tygerberg Hospital[24]. Since 2010, studies of splenectomy that included patients of all ages, showed initial response rates of 83% to 97% decreasing to 59% after a median 20-year follow-up[27]. Conclusions on the role of splenectomy in children cannot be drawn from the current

literature as studies do not separate results by age or disease duration[9]. Moreover, systematic studies of bleeding response to splenectomy have not been performed. In this study, no predictive factors were identified to indicate which patients would require or benefit from early splenectomy. Individual choices of immunosuppressive therapies for ITP have also little evidence or only moderate efficacy with relatively high relapse rates and safety concerns.

In our study, there were similarities in adverse effects in children with primary chronic ITP on medical immunotherapies with or without splenectomy. With appropriate prior vaccinations, followed by prophylactic antibiotics, splenectomy appears to be a safe therapeutic option for children who require treatment beyond first and some second-line therapies [9]. The reported mortality rate post splenectomy in ITP is less than 1%, and is mainly due to peri-operative bleeding [28]. Splenectomy is however associated with a lifelong risk for life-threatening bacterial sepsis, historically at a rate of 0.73 per 1000 patient-years and for overwhelming sepsis up to 3% in children[6]. Modern-day immunizations and sepsis precautions have reduced this risk significantly[26, 29]. In a retrospective study of paediatric patients who underwent splenectomy at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hopital, no cases of overwhelming post-splenectomy infection were noted[21]. Splenectomy may also cause an increased risk for thrombosis and subsequent cardiovascular disease and pulmonary hypertension [9, 23, 30]. Rituximab on the other hand is less well tolerated than other therapies, with infusion reactions occurring in up to 18% of patients and severe or life-threatening intracranial haemorrhage or neurological leukoencephalopathy in up to 4% of patients[7, 17]. In our study, serious adverse effects of Cushing's syndrome, infections, blood dyscrasias, hypertension and gastrointestinal bleeds were seen in children with and without splenectomy as both groups were on corticosteroids and other immunosuppressive therapies as well.

The major limitations of the study were its retrospective and descriptive nature. Comparison of the different therapeutic modalities was not possible as each was performed at different time points and for varying reasons. Furthermore, the time to response to a combination of immunotherapies could not be measured as there was overlap with the different options. Also, patient-reported outcomes, including health-related quality of life assessments were not performed. The strength of this small data set was the electronic storage of clinical and laboratory information which minimized missing data.

In conclusion, the management of persistent/chronic ITP remains difficult with patients responding to a variety of combination medical and surgical therapies with complete response occurring in half the cases and often by 12 months from diagnosis. Sequential choices of secondary therapies should be based on availability of treatment options, costs, social circumstances, and medicine safety. Serious adverse events can occur, and patients need to be monitored closely. Splenectomy remains a therapeutic option in LMICs.

FUTURE RESEARCH RECOMMENDATIONS

1. Comparative effectiveness of second-line therapeutic options in low-resource settings, including evaluation of time to response and health-related quality of life.
2. Investigation of predictive factors to identify patients who would require or benefit from splenectomy early in the treatment process.

AUTHORSHIP

CZ designed the research, collected data, analysed and interpreted data, and wrote the manuscript; YG designed the research; PJ designed the research, interpreted data and edited the manuscript.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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APPENDICES

1. **Proposal submitted to Ethics, accompanying Kids' ITP tool, consent, and assent forms.**

2. **Approval letters.**

3. **Data collection tool.**

Appendix 1: The final Study Protocol

Title

Secondary treatments for paediatric patients with persistent or chronic ITP.

Researcher: Dr CN Zwane

Supervisors: Professor PM Jeena

Dr Y Goga

Introduction

Immune thrombocytopenia (ITP) is a rare, acquired autoimmune condition characterized by a low platelet count and an increased risk of bleeding in children. Although many children with ITP will not need therapy beyond historic first-line treatments, some will require secondary therapy. Despite the establishment of standard guidelines for diagnosis and response criteria, selecting secondary treatments remains a challenge. There is a paucity of published literature with regards to secondary therapeutic modalities.

Immune-mediated thrombocytopenia is defined as isolated thrombocytopenia (peripheral blood platelets < 100 x 10^9/L) in the absence of other causes of thrombocytopenia. It is a diagnosis of exclusion. It is the commonest acquired cause of low platelet counts in childhood, affecting 4–8 per 100 000 children each year at a mean age of 5.7 years at presentation. [1]Platelets are an essential component of vascular integrity. Thrombocytopenia or impaired quality and functioning of platelets increases the risk of bleeding[1]. Depending on the site, frequency and extent of bleeding, this can have a significant impact on health. Although many children with ITP may have a low risk of bleeding, thrombocytopenia can impact the quality of life of such patients,including parental anxiety, social isolation, sporting restrictions, and compromised school attendance.

In most children, ITP is an acute disease, and the thrombocytopenia resolves within a few weeks to months. Overall, less than 25% of affected children have persistent (3-12 months) and chronic ITP (beyond 12 months of presentation)[2]. Children with chronic ITP are at risk of bleeding and they require treatment. Many controversies in its management are recognized with optimal secondary treatment options being unclear. Studies comparing treatment options are scarce, and outcome measures used across studies are inconsistent, despite the

establishment of standard guidelines for both diagnosis and response criteria[3]. Novel therapies for ITP continue to expand, and selecting secondary treatments remains a challenge. Recommendations on available therapies vary internationally, and not all treatment options are readily available in many countries. Splenectomy is the only method that can change the course of the disease as it is associated with long-term, treatment-free remissions; however, the postoperative risk of infection is a deterrent to its routine use[4]. The ITP international working group (ITP-IWG) recommends that splenectomy only be considered in children who have failed all medical therapies, 12 to 24 months from diagnosis as there is the possibility of response to treatment over time[4]. The ITP-IWG recommends a treatment goal of a safe platelet count with the absence of bleeding and not a normal platelet count[5]. Despite these guidelines, clinicians and investigators have varying ideas of platelet response to treatment[3].

Multiple studies support the chronic use of thrombopoietin receptor agonists in children with persistent/chronic ITP where a reduction in bleeding frequency and an absence of adverse effects are seen. When there is no response to thrombopoietin receptor agonist or where there is a loss of response, the American Society of Haematology recommends switching to an alternate thrombopoietin receptor agonist possibly in combination with an immunosuppressant. In those who fail TPO-RAs, especially adolescent females, rituximab and dexamethasone could be considered[4]. Direct comparison between individual treatments is challenging due to the lack of uniform treatment response criteria in published clinical trials and case reports[3].

The American Society of Haematology, International Consensus Document and British Society of Haematology differ on recommendations for secondary treatments including the role and timing of splenectomy, as well as the timing of thrombopoietin receptor agonists.

	International consensus document (Provan 2019)	**British Society of Haematology (Cooper 2014)**	**American Society of Haematology (2019)**
Rituximab	Used with success in children with chronic refractory ITP. Well tolerated	Not recommended due to toxicity to the immature immune system, especially with repeated doses No significant toxicity with a single course.	Suggested over splenectomy, but not over thrombopoietin receptor agonists. Less likely to induce remission. Increasing concern about persistent hypogammaglobulinemia associated with its use
Splenectomy	Effective treatment with previous appropriate vaccinations Rarely indicated.	Still has a role in the management of children with chronic ITP.	To be avoided in the pediatric population, given that children are likely to

	Should only be considered in children who failed medical therapies. Avoided before 5 years of age		undergo spontaneous remission. Thrombopoietin receptor agonists and rituximab preferred over splenectomy.
Thrombopoietin receptor agonists	Supported as the second line. Switch to an alternative TP-RA if poor/no response or add immunosuppressant.	Lack of data in paediatrics, and their effects on young bone marrow Long-term safety evaluations are needed.	Supported as second-line treatment of choice for children with non-life-threatening mucosal bleed and/or diminished health-related quality of life.
Immunosuppressants e.g., azathioprine	Use as add on to thrombopoietin receptor agonist. Lack of data in both adult and paediatric populations.	Immediate side effects and require further evaluation.	Lack of data, no recommendations.
Dexamethasone	No recommendations.	Not recommended as secondary therapy.	Suggested over splenectomy, but not over thrombopoietin receptor agonists.Equivalent to rituximab

Literature review

The published literature was searched using Pubmed and Google scholar using the terms chronic and persistent ITP, treatment response, splenectomy, dexamethasone, azathioprine, thrombopoietin receptor agonists and rituximab.

The goal of this literature review is to compare secondary treatments according to important outcome measures including recurrent bleeding, health-related quality of life, fatigue, as well as platelet response.

Secondary treatment options include:

A. Splenectomy

The spleen is the primary site of platelet destruction. It is an important organ for B-cell development and diversification of the T-cell repertoire. Splenectomy is the most predictable method for achieving a durable remission among patients with chronic ITP[3]. Seventy to eighty percent of children will initially respond to splenectomy; however, the postoperative risk of infection has been a deterrent to its routine use. With appropriate prior vaccinations, followed by prophylactic antibiotics, splenectomy is an effective treatment for paediatric patients who require treatment beyond first-line therapy of ITP[4].

Platelet response

In ITP, splenectomy can achieve high and durable response rates. Since 2010, studies that included adults, as well as children/adolescents, reported initial response rates of 83% to 97% decreasing to 59% after a median 20-year follow-up[5]. Firm conclusions on splenectomy in children cannot be drawn from the current literature because studies do not separate results by age or disease duration[4].

Bleeding response

Systematic studies of bleeding response to splenectomy have not been performed[3].

HRQoL and fatigue response

HRQoL was studied using ITP-PAQ scores in a small sub-analysis of adults with ITP pre- and post-splenectomy (n =13), and no change was found. A Web-based support group survey found that patients with splenectomy had lower ITP-PAQ scores for the domains of work, psychological, fear, and social activity compared with non-splenectomies adults. The overall response to splenectomy was not reported, and the cohort may have been biased by being derived from a support network[6]. There are no studies that report on HRQoL or fatigue post-splenectomy in children.

Safety and tolerability

The reported mortality rate for splenectomy for ITP is less than 1%, mainly as a result of peri-operative bleeding[7]. Short-term complications of splenectomy include bleeding, local infection and thrombosis. Splenectomy is associated with a lifelong risk for life-threatening bacterial sepsis, historically at a rate of 0.73 per 1000 patient-years[3]. Modern-day immunizations and sepsis precautions have reduced this risk significantly. Evaluation for underlying immunologic disorders, such as autoimmune lymphoproliferative disorder, and secondary ITP before splenectomy is critical as there is an increased risk of overwhelming sepsis and death in these patients[8]. Splenectomy may also cause an increased risk for thrombosis and subsequent cardiovascular disease and pulmonary hypertension. However, most of these studies have been in conditions associated with hemolysis, and not in ITP.

B.Rituximab

Rituximab is an anti-CD-20 monoclonal antibody, used in a wide variety of autoimmune conditions including ITP. It causes a rapid depletion of CD-20-positive B cells which are responsible for antibody production, a decrease in serum immunoglobulin levels, and an increased number of T-regulatory cells[3]. It depletes short-lived plasma cells but does not affect long-lived plasma cells. Effects of rituximab last for about 6-12 months.

Rituximab is not approved for the treatment of ITP; however, studies report that it may induce responses in children with chronic ITP[4]. The optimal dose for ITP is still not known.

Platelet response

In a study of 66 children with ITP who were treated with rituximab; 57% had an initial response, but only 26% maintained that response at five years post-treatment[9]. Responses waned over time with durable remission rates of 21% to 26% at five years[9].

Bleeding response

Studies comparing the response to treatment with rituximab other treatment methods are limited.

HRQoL and fatigue

A sub-study of 16 adults with chronic ITP treated with rituximab using the ITP-PAQ scale scores found no change in the HRQoL, before and after treatment[10]. A randomized trial using the SF-36 found that rituximab had no impact on the physical or mental quality of life compared with placebo[11]. Furthermore, 22% of patients who received rituximab reported fatigue compared with 8% of patients who received placebo.

Safety and tolerability

Rituximab may be less well tolerated than other therapies, with infusion reactions occurring in up to 18% of patients. Severe or life-threatening adverse events are reported in up to 4% of patients. These are likely an overestimate resulting from a lack of a causal relationship between rituximab and certain fatal events such as intracranial haemorrhage as well as neurological leukoencephalopathy[12].

Rituximab is administered intravenously every week as opposed to other medical treatments that are administered daily. This may make it a more appealing option, especially in those whom compliance is challenging.

C. Azathioprine

Although azathioprine has been widely available and used to treat ITP for decades, there is no original research data on its efficacy in improving bleeding, or its effects on HRQoL, and fatigue[3]. Although it may be safer or possibly equally effective as other better-studied therapies, use of azathioprine is more challenging in the absence of data.

D. Dexamethasone

Most articles published on the treatment of acute and chronic ITP patients using dexamethasone had small sample sizes.

In 1994, Anderson et al. reported success in treating adults affected by chronic ITP with brief, repeated courses of dexamethasone therapy. This was based on the assumption that at high doses, dexamethasone is capable of suppressing or even eradicating the population of plasma cells responsible for the continued production of anti-platelet antibody. In this study, ten adult patients with chronic refractory ITP were given repeated short courses of high dose dexamethasone therapy (i.e., 40 mg/day for four consecutive days every four weeks). A permanent increase in platelet count with only minimal side effects was reported.

A similar study was performed in children three years later using an equivalent daily dose of 20 mg/m 2 while retaining the same schedule of administration, namely four consecutive days every four weeks for a total of six courses. Contrary to the observations in the adult series, this therapy was not uniformly effective, nor was it well tolerated in the pediatric population. The response rate was only 35% at one month after completion of treatment and decreased to 29% one year later[13]. Patients who had the disease for more than 30 months, did not respond to dexamethasone, suggesting that the treatment is not efficacious in patients with long-standing disease.

In a study on the effectiveness of pulsed high-dose oral dexamethasone therapy in children in 2002, investigators enrolled thirteen children with chronic ITP from an outpatient pediatric clinic. At the end of 6 cycles, three patients showed a complete platelet response, and four patients showed a partial response. Long-term remission was obtained in nearly half the patients with well-established chronic ITP[14]. Although adverse effects including nausea, vomiting, insomnia, anxiety and transient glucosuria were reported; they were not severe enough to result in treatment discontinuation. The authors concluded that given the effectiveness in almost half the patients, minimal side effects, and low cost, dexamethasone should be considered in patients with chronic ITP before considering splenectomy.

Dinesh et al. conducted a study to assess the efficacy of short-course high-dose in children with chronic ITP in 2010. 13 patients with chronic ITP were given HDD-SC (20 mg/ m2 IV daily for four days, for four cycles, repeated every 15 days) for ten months.[15] Of the 12 patients who could be evaluated, there was a complete response in eight patients (66.6%), moderate response in two (17%) patients, and no response in two (17%) patients. A median relapse-free duration of 5 months was observed. They concluded that short-course high-dose dexamethasone was a safe and effective therapy in chronic ITP.

E. Thrombopoietin receptor agonists

The thrombopoietin receptor agonists (TPO-RAs) bind to and stimulate the thrombopoietin receptor to increase platelet production. These agents are not considered curative based on their mechanism of action[3]. Eltrombopag and romiplostim have been studied extensively with regard to their effect on platelet count, bleeding, fatigue, and HRQoL in children. The Food and Drug Administration, as well as the European Medicines Agency, have licensed eltrombopag use in children older than one year with chronic ITP. A retrospective study of TPO-RAs in children with ITP (primary/secondary and newly diagnosed/chronic) reported a durable partial response (platelet count of >30 and at least 2-fold increase the baseline count and absence of bleeding) rate of 40%[16]. A complete treatment response is a platelet counts of >100 for 30 days and the absence of bleeding. These agents are extremely costly and not readily available in all countries.

Eltrombopag

Eltrombopag must be taken on an empty stomach. The starting doses are 25mg daily for children under six, and 50mg daily for children over six years of age. The dose can be titrated up to 75mg daily to maintain optimal platelet count. Dose reductions are needed for patients with hepatic impairment.

Platelet response

Randomized trials in children and adults have demonstrated an initial platelet response of 59% to 75%, with eltrombopag and a durable response of 62% with continued treatment in chronic ITP[17]. The PETIT 1 and PETIT2 studies of eltrombopag in children with chronic ITP reported a platelet count of more than 50 at least once; in 80% of patients; in PETIT2, 40% of patients had a platelet count of more than 50 for more than six weeks without rescue (defined as a composite of new ITP medication or platelet transfusion). Although eltrombopag is not thought to induce remission of ITP, several case series report patients with remission after eltrombopag[3].

Bleeding response

An analysis of 5 eltrombopag trials reported a decrease from baseline in bleeding of between 50% to 73% for eltrombopag-treated patients overall; by week 2, bleeding had decreased from baseline between 26% to 39%. This trend was maintained throughout the study period[18]. No grade 3 or 4 bleeding was reported in patients on eltrombopag in the PETIT trials[16].

HRQoL and fatigue response

Early trials did not show a change of SF-36-measured HRQoL in adults treated with eltrombopag compared with those receiving placebo. However, the later RAISE trial showed significantly greater improvements from

baseline in the SF-36v2 (physical, emotional, and mental function) and Functional Assessment in Cancer (FACT) thrombocytopenia scale were seen in eltrombopag-treated patients[19].

Patients receiving eltrombopag also demonstrate an improvement in vitality, a marker of fatigue on the SF-36v2, compared with those receiving placebo.[18] Of note, however, fatigue was also reported as an adverse event in eltrombopag trials. In PETIT1, children receiving eltrombopag had a small improvement in the Kids' ITP Tool score but did not meet criteria for the minimal important difference[18]. Thus, the effect of eltrombopag on HRQoL in children with ITP is not clear.

Safety and tolerability of TPO-RAs

Eltrombopag is generally well-tolerated, but its absorption is affected by food and dairy, and it must be taken 1 hour before or 2 hours after a meal and at least 2 hours before dairy. This makes administration more difficult for some patients. Major adverse effect concerns include bone marrow reticulin formation (around 2%) and thrombotic events (around 4%)[20]. Data suggests that the increased bone marrow reticulin may be reversible with discontinuation of the drug; however, only a small number of patients with increased reticulin have been evaluated off-therapy[20]. Eltrombopag can be associated with hepatotoxicity 2% (~10% rate of transaminitis) and cataract formation (approximately 5%), which occurred almost exclusively in patients with prior chronic corticosteroid use.

Aim

To determine whether any of the secondary therapies utilised have any advantages in the management of paediatric patients with persistent and chronic ITP.

Objectives

To describe the effectiveness (recurrent bleeding, health-related quality of life, fatigue and platelet response) safety, tolerability, referral adherence and cost of secondary treatment in patients who failed primary therapy at a central haematology centre.

Study design

Observational, retrospective, descriptive study with prospective administration of a HRQoL questionnaire

Study population and sampling

All children (aged between one and sixteen years) diagnosed with persistent and chronic ITP.

Inclusion Criteria

1. Patients aged between one and sixteen years.
2. Patients with persistent or chronic ITP (primary immune thrombocytopenia), defined as a clinical history of mucocutaneous bleeding, absence of splenomegaly and laboratory data confirming isolated thrombocytopenia (platelet count less than 100) for longer than three months
3. Patients managed with one of the secondary therapeutic options, who have regular follow-ups.

Exclusion Criteria

1. Patients with acute ITP
2. Patients with secondary ITP or with immune thrombocytopaenia due to HIV

Sample size

Persistent and chronic ITP in children is a rare condition. The study proposes to include all children treated at Inkosi Albert Luthuli Central Hospital in the past 10 years for this condition. It is anticipated that the number is approximately 30.

Data collection and methods

A list of paediatric patients treated for persistent and chronic ITP at Inkosi Albert Luthuli Central Hospital will be extracted from the pediatric haematology registry. Their clinical electronic records will be accessed using the electronic Meditech filing system at Inkosi Albert Luthuli Central Hospital(IALCH).

A data capturing tool will be used to capture demographics, interventions, the number of presentations to health facilities with bleeding episodes, platelet count and lymphocyte count responses to the various secondary treatment therapies, as well as the frequency of follow-ups.

The Kids' ITP tool, which is used to measure health-related quality of life, will be completed by parents who continue to follow up at our centre. Telephonic interviews will be conducted for those patients who have been discharged from the clinic. The tool is modified as this is a retrospective study, and some questions may not be answerable in retrospect. (see appendix 1) Informed consent /assessment will be obtained from parents and patients for study enrollment in those patients who will be completing the HRQOL questionnaire.

Data Handling

The clinical data will be captured on an appropriate Microsoft Excel spreadsheet. No names will be attached to each data set to maintain patient confidentiality. A study number will be created for each data set to allow for identification in future, should verification be required. All data will be stored on a password protected universal serial bus (USB) and personal laptop.

Outcome measures

Primary outcomes:

1. **For effectiveness**

   we will look at:

   - **Platelet response**

   Definitions:

   - Response:

   Complete platelet response: Platelet count >100 and absence of bleeding

   Partial platelet response: Platelet count >30 and at least 2-fold increase the baseline count and the absence of bleeding

   No response: Platelet count <30 or less than 2-fold increase of baseline platelet count or bleeding

   - Time to response:

   Time from starting treatment to time of achievement of partial and then complete response. Timing of assessment of response to ITP treatments is variable and depends on the type of treatment. The following standardised durations (***Blood*** **(2009)113 (11):2386-2393)** will be used to evaluate the timing of response per secondary treatment option.

Treatment	Time to initial response	Time to peak response
Rituximab	7-56 days	14-180 days
Splenectomy	1-56 days	7-56 days
Azathioprine	30-90 days	30-180 days
Thrombopoietin receptor agonists	7-28 days	14-90 days

   - **Health-related quality of life**

   - **Bleeding response**

Secondary outcomes:

1. Adherence will be measured by using a modified Kids' ITP tool (self-reported questionnaire) and electronic clinic follow-up records at Inkosi Albert Luthuli Central Hospital.

2. A cost-effective analysis of therapeutic interventions that have been used in our centre will be completed. Cost of thrombopoietin-receptor agonists will be extrapolated from private-sector data in South Africa for cost minimization effects as this therapy is currently not available in the public sector in South African.

3. Electronic patient medical records will be reviewed to evaluate predefined adverse effects and complications of treatments received.

4. Quality of life will also be measured using the modified Kids' ITP tool as mentioned above.

Statistical methods

Descriptive statistics will be used to summarize the data. Frequencies and percent will be used for categorical data such as sex, treatment. Frequency distributions of numeric data will be examined for normality and means(sd) or medians(IQR) used as appropriate. Patient outcome will be classified into sub groups according to platelet response: complete, partial or no response at three time points: initial, 6 months and 1 year follow up. At each time point, outcome will be compared by demographic and clinical characteristics: age, sex and comorbidities using chi square tests.

Health related quality of life will be assessed using the modified Kids' ITP tool which is a questionnaire measured on a Likert scale. Total score will be the sum of the question scores. The median total score will be compared by outcome using Kruskal-Wallis rank test. Stata V15 statistical software will be used in the analysis

Ethical considerations

Anonymity and confidentiality

The anonymity and confidentiality of patients will be preserved by not revealing their names and identity in data collection, analysis and reporting of study findings. Preliminary data confirms adequate numbers of cases to undertake the evaluation

Informed consent

Informed consent/assent to participate in a study will be obtained by completing a written form when filling in the questionnaires or verbally when participating in telephonic interviews, from patients and their parents.

Beneficence

Reviewing and evaluating different second-line treatment using up-to-date outcome measures will help clinicians and patients make better-informed decisions, and hopefully improve outcomes of immune thrombocytopenic purpura.

Time frame:

Ethics submission will be by the 05th February 2021

Data collection will commence as soon as BREC approval is received.

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KIDS' ITP TOOLS

Child Self-Report of Quality of Life

Your initials: _____ Your D.O.B: _____

KZ number: _____ Date: _____

INSTRUCTIONS:

For this questionnaire, we are asking; How much of a problem has treatment been for you or your child? Record your answer by putting a tick in the box of the most correct choice. For parents whose children are too young, please mark the answers that you think your child would select.

What do the answers mean?

Answers Meaning

Never = none of the time

Rarely = almost none of the time

Sometimes = once in a while

Often = almost all of the time

Always = all of the time

In general, on this treatment	Never	Rarely	Sometimes	Often	Always
1.I felt poorly					
2. I had a headache					
3. I felt tired					
4. I felt upset (sad or angry)					
6. I felt anxious (worried or nervous or afraid)					
7. I was more hungry than usual					

In general, on this treatment	Never	Rarely	Sometimes	Often	Always
8. I was bothered that I could not do things with my friends					

9. I was bothered because I could not do the activities I like					
10.I was bothered by how much my parents watched me					
11. I was bothered that I didn't know how long my ITP would last					
12. Iwas bothered that I could not do anything to get better					
13. I worry about my platelet count					
14.I worry about my ITP getting worse					
15. I worry about having a more serious disease…					

Please Note: the next set of questions have an additional answer.

On this treatment,	Never	Rarely	Sometimes	Often	Always	
16.I was bothered by my bruises						I did not have any bruises
17.I was bothered by changes in how I looked						I did not have any changes in how I looked
18.Staying overnight in the hospital bothered me						I hardly got admitted
19.Going to clinic often bothered me						I hardly had to go to clinic

20.Having my treatment through a drip bothered me						I did not have treatment through a drip
21.Taking medicine by mouth bothered me						I did not take medicine by mouth
22.I was bothered by missing school						I never had to miss school
23.I worry that I might need to have a bone marrow test						

Was there anything else that bothered you?

_____

_____

_____

Thank You!

<u>Information Sheet and Assent to Participate in a Questionnaire survey</u>

Secondary treatments for paediatric patients with persistent or chronic immune thrombocytopenia

PART 1: Information Sheet

Dear Patient

My name is Dr Collen Zwane, I am doctor training at the University of KwaZulu Natal and Inkosi Albert Luthuli Central Hospital to become a child specialist. I am doing a research study on treatments for children with a disease called persistent/chronic immune thrombocytopenia. Immune thrombocytopenia is a disorder that can lead to easy or excessive bruising and bleeding. The bleeding results from unusually low levels of platelets- the cells that help blood clot.

A research study is when people like me collect a lot of information about a certain thing to find out more about it. I would like to tell you about this study and ask if you will take part in it.

We are inviting you to take part because you live with persistent/chronic immune thrombocytopenia and you have been given some of these medications.

Before you decide if you want to be in this study, it's important for you to understand why we're doing the research and what's involved.

We are doing this study to find out more about the treatments that are given to children with your condition. We are hoping to see if one works better than the other.

If you agree to be in the study and your parents give permission, we will ask you and your parent/guardian to complete a questionnaire related to the benefits and harms of the treatment you received. Each question has four possible answers, and you need to choose one that best describes how the treatment made you feel, how it affected your schooling, and life in general. It will take less than an hour to fill. If there are medications that do not know you have taken or not when mentioned, just write don't know and don't answer any questions related to this.

You will not be paid for being in this study.

There is no benefit to you personally for taking part in this study. But we hope that the results of the research will improve ways in which we treat children with the similar condition.

You might get bored or tired and decide that you don't want to finish the study activities or the interview. If so, just tell us that you want to stop.

A possible risk for any research is that people outside the study might get hold of confidential study information. We will do everything we can to make sure that doesn't happen.

Besides you and your parents, the researchers are the only ones who will know the details of your study participation. If we publish reports or give talks about this research, we will not mention any details related to you. We will not use your name or any other personal information that would identify you.

We will give your study data a code number and keep it in a file with a password that only the researchers know. The file will be on a computer that only the researchers are allowed to use.

Research is something you do only if you want to. No one will get mad at you if you don't want to be in the study. And whether you decide to participate or not, your doctors will still take care of you.

You may stop being in this study at any time. Remember, being in this study is up to you.

We will also ask your parent(s) or caregiver to give their permission for you to take part in this study. But even if they say "yes," you can still decide not to do this.

You can talk to me, or your parents, or someone else at any time during the study.

You can ask any questions that you have about the study. If you have other questions later, you can call me or ask me next time you see me.

You can contact me on 031 240 1000 or e-mail :209519314 @stu.ukzn.ac.za.

If you decide to participate, and your parents agree, we'll give you a copy of this form to keep for future reference.

PART 2: Certificate of Assent

I agree to take part in the questionnaire activity.

OR

I do not wish to take part in the research, and I have not signed the assent below. _____ (initialed by child/minor)

Only if child assents:

Print name of child: _____

Signature of child: _____

Date: _____

Name of translator (where applicable): _____

Signature: _____

Date: _____

If illiterate:

I have witnessed the accurate reading of the assent form to the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness (not a parent) _____ AND Thumb print of participant

Signature of witness _____

Date _____

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the child understands that the following will be done:

A questionnaire will be given to child and guardian for them to fill.

I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Print Name of Researcher/person taking the assent_____

Signature of Researcher /person taking the assent _____

Date _____

Copy provided to the participant _____

Parent/Guardian has signed an informed consent ___Yes ___No _____

Information Sheet and Consent to Participate in a Questionnaire Survey

Information Sheet:

Dear Parent/guardian

My name is Dr Collen Zwane, I am a doctor training at the University of KwaZulu Natal and Inkosi Albert Luthuli Central Hospital to become a child specialist. I am doing a research study on treatments for persistent/chronic immune thrombocytopenia.

Immune thrombocytopenia is a disorder that can lead to easy or excessive bruising and bleeding. The bleeding results from unusually low levels of platelets-the cells that help blood clot.

In most children, it is a disease that usually starts and end within the first episode (acute presentation), and the low platelet count resolves within a few weeks to months with initial treatment. Some children unfortunately end up with more long standing disease needing more (secondary) therapy. Low platelet count can impact the quality of life of your child by social isolation, sporting restrictions, compromised school attendance and your anxiety. Selecting these additional treatments remains a challenge for clinicians as there is no studies comparing them.

The purpose of this study is to determine if any of these additional treatments used in our centre for treating children like yours who did recover from the first episode have any advantages or harms. this questionnaire survey may help us decide which of the treatment are good and which are not so.

You and your child are being invited to participate in this questionnaire survey because he/she lives with this long-standing disease. There are other similar cases that we are hoping to enroll onto this study.

Participation in this study is entirely voluntary. Refusing to participate will not affect your child's treatment in anyway. He/She will still have all the benefits that they would otherwise have. We will also discuss this research with your child and if they refuse to participate, their refusal will be respected, even if you have agreed to participate.

Moreover, if you do agree to take part, you may change your mind at any time and for any reason by letting the researcher know using the contact information below:

Telephone number: 031 240 1000

E-mail address: 209519314@stu.ukzn.ac.za.

Your child care will not be affected with you refusal to be in the study

You and your child will be asked to complete a survey regarding concerns, challenges, and benefits of treatment that your child received, anonmyously. To make it easy we have provided four possible answers for each question. You and your child will need to choose the answer that you feel best describes what you think or how you feel. We want to know about the possible harms that the child might have experienced on the treatment, how you felt about the frequency of clinic visits, whether treatment was easy to take, if it caused any distress and how the child's illness and treatment affected the child's schooling and social life.

The survey should take less than an hour to complete.

We will keep this document separate from your completed survey such that there will be no way to connect survey responses with individual respondents.

If we publish reports or give talks about this research, we will only discuss group results. We will not use your child's name or any other personal information that would identify him/her.

The completed surveys and this signed document (consent form) will be kept in a locked filing cabinet. After collection, the data will be entered into a password-protected file on a computer and stored on a private password-protected computer to which only I will have access to.

There are no risks from participation in this study. Various steps will be taken to maintain strict confidentiality.

There will be no money paid for participating in this study, but we can help you get to IALCH to complete the questionnaire.

The anticipated benefits from participating in this research is the contribution to the advancement of scientific knowledge and betterment of care. We may be able to benefit other children and maybe you, should we find that one treatment is better than the other. We will let you know of the findings of the research by a telephone call.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number_____).

Should you have any questions/concerns about your child's rights as a research participant, please contact the researcher at 031 240 1000 / 209519314@stu.ukzn.ac.za or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2602486 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

If you agree to be in a research, you will be asked to provide a signature at the bottom of the next page signifying that you understand the information contained in this consent form.

DECLARATION OF CONSENT

I _____have been informed about the study entitled Secondary treatments for pediatric patients with persistent or chronic ITP by Dr Collen Zwane.

I understand the purpose and procedures of the study.

I have been given an opportunity to ask questions about the study and have been answered to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that my child would usually be entitled to.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at 031 240 1000 or 209519314@stu.ukzn.ac.za.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2602486 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

_____ _____

Signature of Participant **Date**

_____ _____

Signature of Witness **Date**

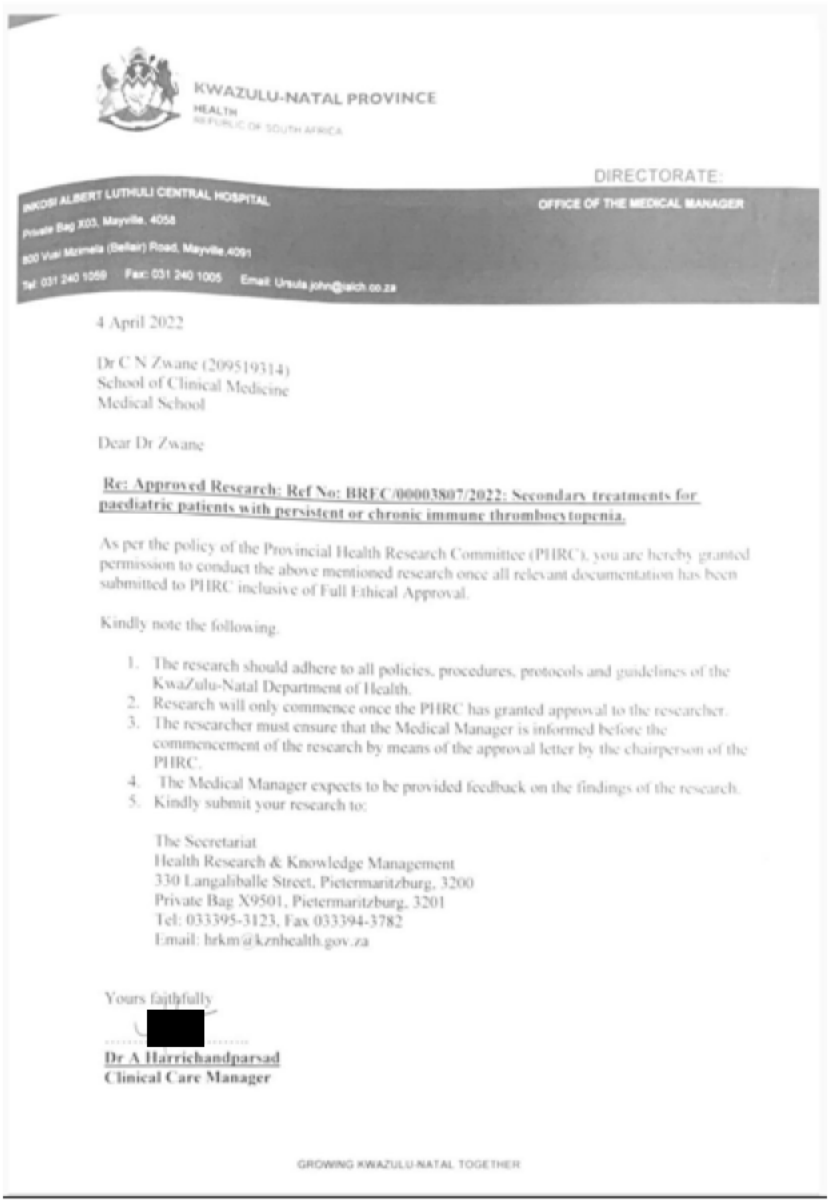
(Where applicable)

_____ _____

Signature of Translator **Date**

(Where applicable)

Appendix 2: Ethical approvals



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
OFFICE OF THE MEDICAL MANAGER

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
Private Bag X03, Mayville, 4058
800 Vusi Mazinyela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@alch.co.za

4 April 2022

Dr C N Zwane (209519314)
School of Clinical Medicine
Medical School

Dear Dr Zwane

Re: Approved Research: Ref No: BREC/00003807/2022: Secondary treatments for paediatric patients with persistent or chronic immune thrombocytopenia.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

The Secretariat
Health Research & Knowledge Management
330 Langalibalele Street, Pietermaritzburg, 3200
Private Bag X9501, Pietermaritzburg, 3201
Tel: 033395-3123, Fax 033394-3782
Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr A Harrichandparsad
Clinical Care Manager

GROWING KWAZULU-NATAL TOGETHER

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: [redacted]
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202205_014

Dear Dr CN Zwane
(UKZN)

Approval of research

1. The research proposal titled **'Secondary treatments for paediatric patients with persistent or chronic ITP'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutgé
Chairperson, Health Research Committee
Date: 01/06/2022.

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

28 October 2022

Dr Collen Noluthando Zwane (209519314)
School of Clinical Medicine
Medical School

Dear Dr Zwane,

Protocol reference number: BREC/00003807/2022
Project title: Secondary treatments for paediatric patients with persistent or chronic immune thrombocytopenia
Degree: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 28 October 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 28 October 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 December 2022.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 3: Data collection tools

Demographics	**Age at presentation**				
	Gender	**Male**			
		Female			
	Race	**African**			
		Indian			
Presentation	**Major bleeds**				
	Minor bleeds				
	Incidental finding of thrombocytopenia	**Yes**			
		No			
	Blood results at diagnosis	**Platelets**			
		Haemoglobin			
		White cell count			
	Viral screen	**Positive**			
		Negative			
		Not done			
	BMAT results	**Features of ITP**			
		Not done			
	U/S abdomen findings				
	Pen VK received	**Yes**			
		No			
Therapeutic intervention received **Yes/No**	**Azathioprine**				
	Azathioprine & prednisone				
	Ciclosporin				
	Rituximab				
	Splenectomy		**Pen VK received?**	**Yes**	**No**
			Pre-surgery vaccines received?	**Yes**	**No**
			US abdomen	**Done/findings**	**Not done**
Platelet response at 6 months		**Complete**			
		Partial			
		No response			
		Lost to follow up			
Bleeding at 6 months		**Yes**	**Major**		
			Minor		
		No			
		Lost to follow up			
Platelet response at 12 months		**Complete**			
		Partial			
		No response			

		Lost to follow up	
Bleeding at 12 months		Yes	Major
			Minor
		No	
		Lost to follow up	
Adverse drug reactions Yes/No		Cushings	
		Infections	
		Thrombopoiesis	
		Blood dyscrasias	
		Gastrointestinal bleed	
		Hypertension	
Final outcome		Complete Remission	
		Relapse/no response	
		Lost to follow up	