The Prevention of Glucocorticoid-Induced Osteoporosis in Patients with Immune Thrombocytopenia receiving Steroids: a British Society for Haematology Good Practice Paper

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Methodology

This Good Practice Paper was compiled according to the BSH process at http://www.b-s-h.org.uk/guidelines/proposing-and-writing-a-new-bsh-guideline/. The British Society for Haematology (BSH) produces Good Practice Papers to recommend good practice in areas where there is a limited evidence base but for which a degree of consensus or uniformity is likely to be beneficial to patient care. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

A search for English language literature on glucocorticoid-induced osteoporosis in patients with immune thrombocytopenia (ITP) from 1960 to 2017 was carried out on the 21st November 2017. Ovid Medline, Embase and the Cochrane database of systematic reviews were searched. Details of the search and a summary table of the main findings can be found in Supplementary Appendix 1.

Review of the manuscript

Review of the manuscript was performed by members of the UK ITP Forum, the Committee of Scientific Advisors of the International Osteoporosis Foundation, the British Society for Haematology (BSH) Guidelines Committee General Haematology

Task Force, the BSH Guidelines Committee and the General Haematology Sounding Board of BSH. It was also on the members section of the BSH website for comment. It has also been reviewed by The ITP Support Association, although this organisation does not necessarily approve or endorse the contents.

Introduction

Glucocorticoids are a standard first line treatment for immune thrombocytopenia (ITP) and are an important risk factor for osteoporosis. Glucocorticoids act directly to suppress bone formation by inhibiting osteoblast function and triggering osteoblast (and osteocyte) apoptosis. They also act indirectly by inhibiting intestinal calcium absorption and reducing gonadal hormones. Despite this, current ITP guidelines (3, 4) have not addressed the need to identify patients at high risk of fragility fracture, who would benefit from bone-protective treatment. However, recent guidelines for the prevention and treatment of osteoporosis give recommendations for patients receiving glucocorticoids, irrespective of underlying diagnosis (1, 5) and have been based on systematic review of the literature. In this good practice paper, we conduct a systematic review of the literature on osteoporosis in patients with ITP receiving glucocorticoids, assess the applicability of current guidelines on prevention of glucocorticoid-induced osteoporosis (GIOP) to the treatment regimens used for patients with ITP and make treatment recommendations.

Prevention of osteoporosis in patients receiving glucocorticoids

Fragility fractures, particularly vertebral fractures, occur in up to 30-50% of adults receiving long term glucocorticoids (6). Loss of bone mineral density (BMD) is most rapid in the first 3-6 months but continues to decline at a slower rate with continued

use (5). This is associated with an increased fracture risk, and a meta-regression analysis of randomised controlled trials found that the annual incidence of vertebral fracture was 5.1% in patients who had commenced glucocorticoids ≤6 months previously vs. 3.2% if commenced >6 months ago (7). Loss of BMD appears partially reversible after withdrawal of glucocorticoids and withdrawal leads to a reduction in fracture risk (6) although a residual increased risk persists (8). Fracture in patients receiving glucocorticoids is not solely dependent on bone loss (8) and fractures occur at higher BMD compared to postmenopausal osteoporosis (9). Fracture risk rises with age, and with higher cumulative and daily dose of glucocorticoids. Additional clinical risk factors for fracture that are independent of BMD are listed in table 1 (1). A UK evidence based guideline for osteoporosis prevention has recently been published (1). The guideline considers patients receiving glucocorticoids with an anticipated duration of ≥3 months and some key conclusions are summarised in table 2, although clinicians should refer to the original guideline for full details. The input of an endocrinologist may be helpful for complex cases.

Fracture risk assessment

The management of children and adults <40 was not addressed in detail in the UK osteoporosis guideline. Although fracture risk is lower in pre-menopausal women and men <50, this risk can still be significant in some individuals, for example the 10-year fracture risk has been estimated at 5–20% in pre-menopausal women ≥30 years receiving very high doses of glucocorticoids (5). Other risk factors identified in pre-menopausal women include prior fragility fracture, low BMD, family history of osteoporosis, low body mass index or low weight, age, age at menarche, major

depression and alcohol intake (11, 14-18). Recent American guidelines concluded that BMD testing should be considered in adults age <40 at treatment onset if there were additional risk factors, and bone protective therapy considered in adults <40 if 1) prior fragility fracture 2) receiving ≥7.5 mg prednisolone daily with a Z score < -3 at hip or spine or 10% or more BMD loss/year at hip or spine 3) age ≥30 receiving ≥30 mg prednisolone daily with a cumulative dose >5g in the last year (5).

For patients age 40-90 years, clinical risk factors (with or without a BMD measurement) can be entered into a validated algorithm (FRAX®), available on line at www.sheffield.ac.uk/FRAX/tool.jsp that calculates the 10 year probability of hip fracture or major osteoporotic fracture (i.e. clinical fracture at the spine, distal forearm, humerus or hip). Having calculated the fracture risk on-line, a link is provided to guidance from the National Osteoporosis Guideline Group (NOGG) based on UK intervention thresholds for treatment, that is adjusted for steroid dose (for patients outside the UK, adjustments to FRAX risk based on age and steroid dose can be found in Supplementary Appendix 2). High risk patients should be considered for bone-protective treatment such as an oral bisphosphonate. Patients at low risk can be reassured and provided with lifestyle advice. BMD assessment is recommended for those with intermediate risk and the result entered into the FRAX tool to determine the need for treatment.

Because the intervention threshold is generally exceeded, bone protective treatment can be considered in 1) men or women ≥70 years, and 2) men ≥50 or post-menopausal women with a prior fragility fracture or taking a high dose of glucocorticoids (≥7.5 mg prednisolone), without further risk assessment (1).

Interventions

Interventions for patients at risk of GIOP include lifestyle measures, optimizing calcium and vitamin D intake, and bone protective therapies. The evidence base for lifestyle measures in adults (Table 2) is based on smoking and greater alcohol intake being risk factors for osteoporosis (22, 23) and weight-bearing exercise having a beneficial effect on BMD (24), rather than evidence that these measures will prevent fractures. Two meta-analysis found that for patients receiving glucocorticoids, the combination of calcium and vitamin D supplements was more effective in preserving BMD than calcium alone or no therapy (25, 26). Bisphosphonates (e.g. alendronate, risedronate or zoledronic acid) and teriparatide (recombinant human parathyroid hormone) have been shown to reduce fractures in post-menopausal women with osteoporosis (27-30). They are also licenced for the prevention of GIOP, with evidence of effectiveness in BMD bridging studies (31-34) and subsequently, fracture prevention (19-21). Treatment has also been shown to preserve bone density in pre-menopausal women while data in men age <50 years is limited (11).

Good prescribing practice

Bisphosphonates have a number of contra-indications such as hypocalcaemia, hypersensitivity, severe renal impairment, pregnancy and lactation. Oral bisphosphonates should be avoided in those unable to stand or sit upright for at least 30-60 minutes and those with oesophageal stricture or achalasia. Rare adverse events include osteonecrosis (jaw or external auditory canal) and atypical femoral fractures. Patients should be encouraged to have a pre-treatment dental review, maintain good oral hygiene, avoid dental intervention if possible while on treatment,

and to report dental problems, recurrent ear infections and hip, thigh or groin pain (1). There is inadequate safety data for the use of bisphosphonates in pregnancy and given their long half-life, these should be avoided in women of child bearing potential unless there is a strong indication for treatment (11).

Impact of glucocorticoids in patients with ITP

Our systematic review identified four case series or case-control studies of between 24 and 36 children and one adult series of 18 patients assessing bone mineral density (BMD) after steroids (Supplementary appendix 1). In children, there was a significant negative correlation between BMD and cumulative steroid dose (35-37). In one series, 9/36 (25%) children had osteopenia and one had osteoporosis (36). BMD was significantly lower in children receiving a cumulative dose over 2100 mg/kg compared with those receiving less (35) and a BMD Z-score of less than -2 standard deviations was found in 5/9 children receiving a cumulative dose >1000 mg/kg vs. 0/19 receiving a cumulative dose <1000 mg/kg (37). Different regimens appeared to vary in their impact on BMD but data were insufficient to draw conclusions. In the adult study, the average total (prednisolone equivalent) dose received was 5233 ± 3541 mg. 7/18 (39%) patients had osteoporosis and a significant negative correlation was found between BMD and both total, and mean daily, steroid dose (38). The same study reported on BMD in 32 patients with low bone mass, before and after treatment with the bisphosphonate alendronate, finding a significant increase after 6 and 12 months.

There is no mechanistic reason to think that the impact of glucocorticoids on bone mineral density, or the effects of treatment to prevent osteoporosis should be

different in patients with ITP, as compared to patients with other disorders. The studies reviewed support this.

Recommendation: general guidelines for osteoporosis prevention are applicable to patients with ITP (1C).

Do the glucocorticoid dosing regimens used in ITP impact on the application of osteoporosis guidelines?

Although an arbitrary cut off, some studies have found that fracture risk is not significantly elevated in patients receiving steroids for <3 months (10) and most guidelines are for patients with an intended duration of treatment ≥3 months (5, 11). These guidelines have recognised a daily dose of ≥ 5-7.5 mg oral prednisolone or equivalent as high risk. Research from the United Kingdom GP database found that patients aged ≥40 years receiving high dose intermittent oral glucocorticoids (defined as at least one prescribed daily dose ≥15 mg) but for a short duration (cumulative dose ≤1 g) had only a small increase in the risk of fracture. Risk was substantially increased when the daily dose was ≥15 mg and cumulative dose >1 g. The highest vertebral fracture risk (relative risk 14.4) was with a daily dose ≥30 mg and cumulative dose >5 g (12). A second population based study also found that in patients aged ≥18 receiving a cumulative dose <1 g, the risk of major osteoporotic fracture was not increased (13).

Adults

Glucocorticoids are currently a first line treatment for ITP but relapsing patients may receive repeated courses, either as rescue therapy, in combination with other

treatments, or as low dose maintenance therapy in selected refractory cases (2-4, 39). Newer therapeutic agents for ITP such as thrombopoietin receptor agonists (TPO-RA) have reduced but not eliminated the need for longer term glucocorticoids and in an open label extension study of the TPO-RA romiplostim, glucocorticoids were required in 35% of patients during weeks 1–24, and 20% during weeks 121–144 (40).

Initial treatment is with oral prednisolone 1 mg/kg for between 4 days and 4 weeks followed by a taper over 4-6 weeks (2-4, 41), or with dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles (4, 41). The cumulative steroid dose for typical first line adult regimens is therefore approximately 1-2 g (Table 3). Hence the daily and cumulative doses are high, but the duration is slightly shorter than covered by standard guidelines for glucocorticoid-induced osteoporosis.

Children

In children requiring treatment of their ITP, steroids are often used first line. However paediatric regimens are usually shorter, for example prednisolone 3-4 mg/kg/day for 4 days, or prednisolone 2 mg/kg for 14 days then stopped or tapered over a further 21 days (3, 4) (Table 3). As shown above, some children subsequently receive multiple glucocorticoid courses that result in reduced BMD.

The recommendations below are based on recent UK NOGG guidelines for the prevention and treatment of osteoporosis (1), which are accredited by the National

Institute of Health and Care Excellence (NICE). However, they have been further adapted to consider the typical dose and duration of steroids used for ITP patients.

Recommendations

Initial fracture risk assessment

- **Patients age ≥70 years, or men ≥50 years and post-menopausal women with a previous fragility fracture can be considered high risk and not require further assessment (Figure 1) (2C)**
- **At treatment onset, patients age 40-69 (excluding men ≥50 years and post-menopausal women with previous fragility fracture) should be assessed by FRAX score without BMD assessment at treatment onset (www.sheffield.ac.uk/FRAX/tool.jsp) to define high, intermediate or low risk (2C).**
- **Ideally, those at intermediate risk should have a DXA (dual energy x-ray absorptiometry) scan and femoral neck BMD entered into FRAX to define high and low risk. However in patients receiving a short steroid regimen i.e. ≤12 weeks, particularly when a DXA result is unlikely to be available during treatment, a decision can be made clinically and not all patients require bone-protective treatment (2C).**
- **Adults age <40 years and children do not routinely require DXA assessment (2C).**

Interventions

- **All adults starting on glucocorticoids should be given lifestyle advice to optimise bone health (Table 2) (2C).**
- **Check serum calcium and vitamin D levels (2C)**
- **Adequate daily vitamin D (800 iu) and calcium (700-1200 mg) intake in adults is recommended through diet if possible or supplements if needed, but with a relatively short anticipated duration of treatment, supplements may be the most practical method of ensuring adequate intake (2C).**
- **Patients at high risk of fracture should be considered for an oral bisphosphonate such as alendronate or risedronate. If contraindicated or poorly tolerated, zoledronic acid or teriparatide are appropriate alternatives (1A).**

Patients receiving similar glucocorticoid regimens for relapse

- **Use the minimum necessary dose and consider whether glucocorticoid sparing alternatives are appropriate (2C)**
- **Patients previously treated with bisphosphonates may be re-treated (Figure 2) (2C).**
- **If re-treatment with glucocorticoids is within a year, men over 50 and post-menopausal women may be considered high risk. Other adults ≥40 years should be risk assessed (2C)**
- **Use of bisphosphonates may be appropriate in selected adults <40 years and children, particularly those with a prior fragility fracture or receiving high cumulative doses e.g. ≥1 g/kg in children or ≥5g in adults.**

Measurement of BMD may be helpful in assessment of risk and to monitor the effects of treatment (2C)

Discontinuing bisphosphonates

- **When a patient stops their glucocorticoid, the bisphosphonate can also be stopped following an individual risk assessment. This may include assessment of BMD in patients who have received prolonged therapy (2C)**

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Declaration of Interests

No expenses were incurred during the writing of this good practice paper.
All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. QAH is secretary of the UK ITP Forum and has received honoraria from Novartis and Shire. JDG has received honoraria from

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Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines/).

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

Clinical risk factors for fracture independent of BMD and age
Low body mass index (≤19 kg/m^2)
Previous fragility fracture (e.g. hip, vertebral)
Parental (mother or father) history of hip fracture
Current smoking
Alcohol intake ≥3 units/day
Rheumatoid arthritis
Glucocorticoid therapy

Table 1. Clinical risk factors for fracture
BMD; bone mineral density

Fracture risk assessment in patients receiving glucocorticoids
• Consider bone-protective therapy in men or women ≥70 years, those with a prior fragility fracture and those taking a high dose of glucocorticoids (≥7.5 mg prednisolone). • In other individuals, fracture probability should be estimated using FRAX with adjustment for glucocorticoid dose.
Lifestyle and dietary advice
• Adults should receive lifestyle advice (regular weight-bearing exercise, stop smoking, reduce alcohol intake to ≤2 units/day) • Adults should receive adequate daily intake of calcium (700-1200 mg) and vitamin D (800 iu) through diet if possible or supplements if needed
Bone-protective therapy
• Because bone loss and increased fracture risk occur early after initiation of glucocorticoids, bone-protective treatment should be started at the onset of therapy in patients at increased risk of fracture • Bone-protective therapy may be appropriate in some premenopausal women and younger men, particularly in individuals with a previous history of fracture or receiving high doses. • For adults at high risk of fracture, consider an oral bisphosphonate such as alendronate or risedronate. If contraindicated or poorly tolerated, zoledronic acid or teriparatide are appropriate alternatives • On stopping glucocorticoids, consider stopping bone-protective therapy following an individual risk assessment. This may include assessment of BMD in patients who have received prolonged therapy

Table 2. Summary of recent guidance on the assessment of fracture risk and indications for treatment in men ≥50 and post-menopausal women receiving glucocorticoids for ≥3 months (1)

BMD; bone mineral density

Glucocorticoid regimen	Cumulative (prednisolone equivalent) steroid dose
Prednisolone 1 mg/kg for 21 days then tapered (70 kg)	2520 mg
Prednisolone 1 mg/kg for 4 days then tapered (70 kg)	1330 mg
Dexamethasone 2 cycles of 40 mg daily for 4 days	2133 mg
Prednisolone 4 mg/kg/day for 4 days (30 kg)	480 mg (16 mg/kg)
Prednisolone: 7.5 mg daily for 3 months (84 days)	630 mg

Table 3. Cumulative steroid dose for typical first line ITP steroid regimens compared with threshold duration and dose considered high risk (prednisolone ≥7.5 mg daily for ≥3 months)

For doses in mg/kg, weight used for estimate of cumulative steroid dose is in brackets.

Steroid taper: prednisolone 40 mg daily for 2 weeks, 20 mg daily for 2 weeks, 10 mg daily for 2 weeks, 5 mg daily for 2 weeks then stop (2)

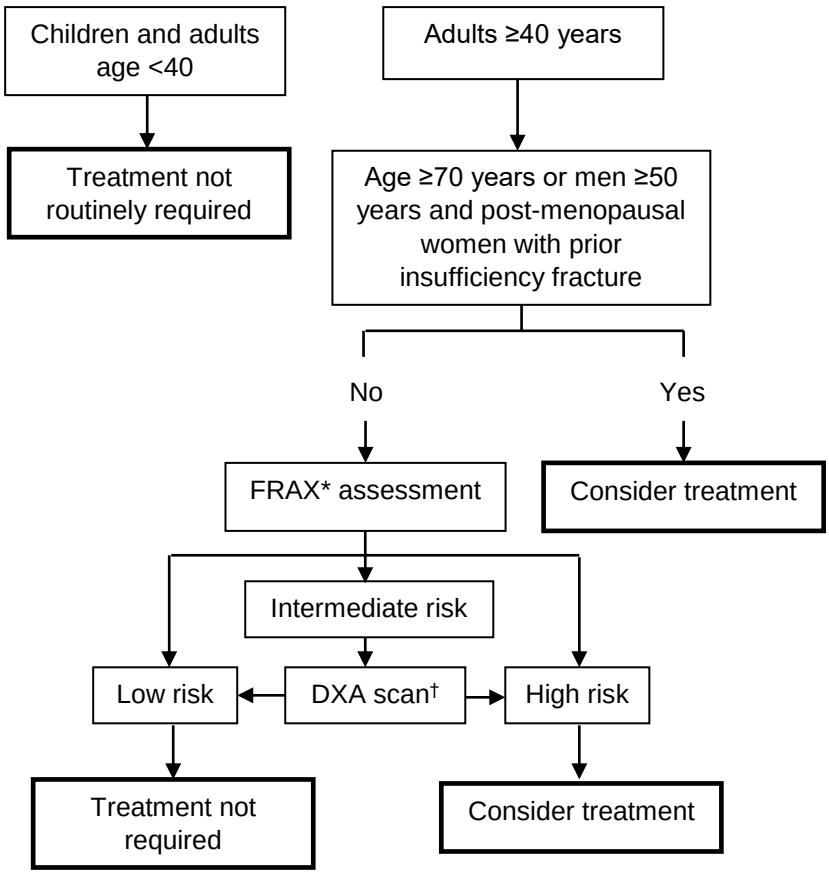

Figure 1. Risk adapted approach to bisphosphonate treatment for patients with ITP receiving first line glucocorticoids

ITP; immune thrombocytopenia, DXA; dual energy x-ray absorptiometry

*FRAX is a fracture risk assessment tool www.sheffield.ac.uk/FRAX/tool.jsp

†Local access to DXA may vary. If a report will not be available during glucocorticoid treatment, a decision should be made on clinical grounds in patients with intermediate risk FRAX.

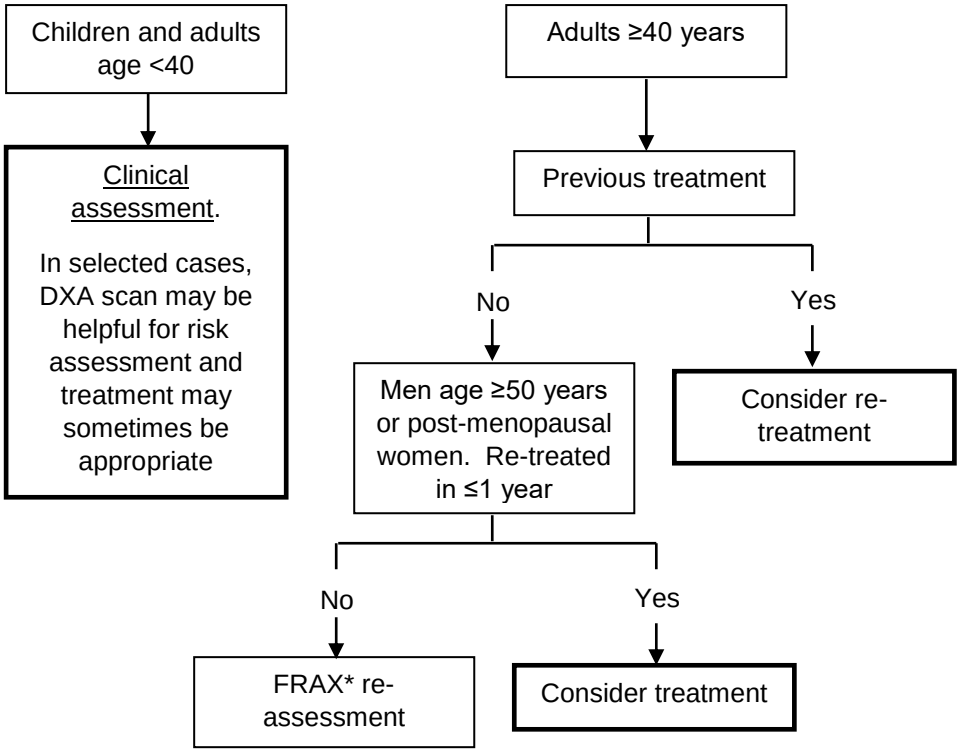

Figure 2. Risk adapted approach to bisphosphonate treatment for patients with ITP receiving retreatment with glucocorticoids

ITP; immune thrombocytopenia, DXA; dual energy x-ray absorptiometry

*FRAX is a fracture risk assessment tool www.sheffield.ac.uk/FRAX/tool.jsp

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