An update of the Malaysian Clinical Guidance on the management of glucocorticoid-induced osteoporosis, 2015

Swan Sim Yeap a,*, Fen Lee Hew a, Premitha Damodaran b, Winnie Chee c, Joon Kiong Lee d, Emily Man Lee Goh e, Siew Pheng Chan a, The Malaysian Osteoporosis Society Committee Working Group for the Clinical Guidance on the Management of Osteoporosis, 2015

a Subang Jaya Medical Centre, Subang Jaya, Selangor, Malaysia
b Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
c International Medical University, Seremban, Negeri Sembilan, Malaysia
d Assunta Hospital, Petaling Jaya, Selangor, Malaysia
e Gleneagles Hospital, Kuala Lumpur, Malaysia

Received 26 October 2016; revised 2 January 2017; accepted 3 January 2017
Available online 18 January 2017

Abstract

Objectives: This Clinical Guidance is aimed to help practitioners assess, diagnose and manage their patients with glucocorticoid-induced osteoporosis (GIO), using the best available evidence.

Methods: A literature search using PubMed (MEDLINE) and The Cochrane Library identified all relevant articles on GIO and its assessment, diagnosis and treatment, from 2011, to update from the 2012 edition. The studies were assessed and the level of evidence assigned. For each statement, studies with the highest level of evidence were used to frame the recommendation.

Results: Consider treatment early in all patients on glucocorticoids (GC) as fracture risk increases within 3–6 months of starting GC. The decision to start treatment for GIO depends on the presence of prior fracture, category of risk (as calculated using Fracture Risk Assessment Tool), daily dose and duration of GC treatment, age, and menopausal status. General measures include adequate calcium and vitamin D intake and reducing the dose of GC to the minimum required to achieve disease control. In patients on GC with osteoporotic fractures or confirmed osteoporosis on dual-energy X-ray absorptiometry, bisphosphonates are the first-line treatment. Treatment should be continued as long as patients remain on GC. Algorithms for the management of GIO in both pre- and post-menopausal women and men have been updated.

Conclusions: In post-menopausal women and men above 50 years, bisphosphonates remain the mainstay of treatment in GIO. In pre-menopausal women and men below 50 years, bisphosphonates are recommended for those with a prevalent fracture or at very high risk only.

Keywords: Glucocorticoids; Corticosteroids; Osteoporosis; Guidelines; Malaysia

1. Introduction

Osteoporosis and fractures are major complications of glucocorticoid (GC) therapy. From epidemiological studies, a significant number of the population are at risk; about 2% of the elderly population use oral GCs in the United Kingdom [1] and in the United States, between 1999 and 2008, 1.2% of the population (in the National Health and Nutrition Examination Survey (NHANES) database) were on GC, with 28.8% taking GC for more than 5 years [2]. Many of the inflammatory conditions that may require GC usage are already associated with an increased risk of fracture [3]. The addition of GC
* For low and medium-risk patients, recommendations are for an anticipated or prevalent duration of > 3 months of glucocorticoid treatment

† See section 3.2.1

Fig. 1. Approach to postmenopausal women and men age >50 years initiating or receiving glucocorticoid therapy [17].
therapy increases risk of sustaining fractures over and above that of the underlying disorder [4] (Level III).

Bone loss occurs most rapidly in the first 6–12 months of oral GC therapy [5], with an increase in fracture risk that appears within 3–6 months of starting GC [5,6] (Level Ia). Thus, it is important to consider bone protective strategies at the onset of GC therapy. Furthermore, at similar levels of bone mineral density (BMD), postmenopausal women taking GCs, as compared with nonusers of GCs, had considerably higher risks of fracture [7] (Level Ib).

Prednisolone ≥ 5 mg daily or its equivalent, for more than 3 months is associated with osteoporosis and an increased risk of fractures [8], but doses of prednisolone ≤ 2.5 mg daily have also been associated with an increased relative risk of vertebral fracture [6] (Level III).

Standard doses of inhaled or topical GC use have not been shown to adversely affect BMD. However, the cumulative inhaled GC dose in asthmatics have been inversely associated with BMD [9] and inhaled high potency GC usage (greater than 1500 μg daily) have been associated with both vertebral [10] and hip fractures [11] (Level IIa).

2. Methods

The previous Clinical Practice Guidelines published in 2012 was used as the baseline. To update the document, a systematic review and literature search by the members of the Working Group, using PubMed (MEDLINE), identified all relevant articles on GIO and its assessment, diagnosis and treatment, from 1st January 2011 to 31st December 2015. The date 2011 rather than 2012 was chosen so that all studies published just before and after the last guidelines would be reviewed and none inadvertently overlooked. The search on PubMed using the keywords “glucocorticoid” and “osteoporosis” during the above time frame, limited by “Human” and “English”, produced 527 articles. Of these, 158 were on osteoporosis in general unrelated to GIO, 131 were studies that did not have any relationship to GIO for example, studies using GC in various diseases, 38 were on childhood GIO/GC usage, and 69 were studies related to the molecular mechanism of action of GC; this left 131 studies that were further assessed for this paper. A search of the Cochrane Library website (www.cochrane.org) from 1st January 2011 to 10th October 2016, just before this manuscript was completed showed 1 new review “Bisphosphonates for treating osteoporosis caused by the use of steroids” published in 5 October 2016.

The studies were assessed by 2 of the Working Group members and those that were used in the Clinical Guidance were graded with the levels of evidence as used by the National Guideline Clearinghouse, Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA [12] (Appendix 1). For each statement, studies with the highest levels of evidence were used to frame the statements. The grade of recommendation was taken from the Scottish Intercollegiate Guidelines Network grading system [13] (Appendix 1).

3. Results and discussion

3.1. Assessing risk and diagnosis

The use of BMD measurement for the diagnosis of GIO is not crucial, but may be useful in the monitoring of therapy. BMD should be measured at the lumbar spine and hip by dual-energy X-ray absorptiometry (DXA), although the lumbar spine measurement may be artefactually elevated in the elderly due to degenerative changes [14]. As there are data showing that postmenopausal women taking GC have a higher fracture risk compared to those not taking GC at a similar BMD [7], a treatment threshold at a T-score of < −1.5 has been suggested [14,15]. Diagnostic thresholds in GIO have not been established for peripheral densitometry using either DXA or ultrasound, which therefore should not be used for assessment or monitoring [14].

The more recent GIO guidelines have used Fracture Risk Assessment Tool (FRAX) [16] to categorise patients into low, medium and high risk groups with respect to the 10-year risk of fracture, rather than relying on BMD measurement alone.

In postmenopausal women and men over 50 years old with low risk of fracture, treatment is recommended when prednisolone (or its equivalent) ≥ 7.5 mg daily is taken for more than 3 months. In medium risk patients, treatment is recommended at any dose of GC when taken for more than 3 months. In high risk patients, treatment is suggested for any dose of GC taken for any length of time [17] (see Fig. 1). In addition to the calculated FRAX risk estimates, Table 1 lists the clinical factors that may shift an individual to a greater risk category for GIO [17].

For premenopausal women of non-childbearing potential and men under 50 years old with a prevalent osteoporotic fracture, treatment is recommended if prednisolone (or its equivalent) ≥ 5 mg daily is given for >1 month. For premenopausal women of childbearing potential, treatment is recommended when prednisolone ≥ 7.5 mg daily is given for >3 months [17] (see Fig. 2).

There has been a recommendation that the FRAX risk estimates should be adjusted according to the daily dose of GC. For low-dose exposure (< 2.5 mg daily of prednisolone or equivalent), the probability of a major fracture is decreased by about 20% depending on age. For medium doses (2.5–7.5 mg daily), the unadjusted FRAX value can be used. For high doses

| Table 1 | Clinical factors that may shift an individual to a greater risk category for glucocorticoid-induced osteoporosis [17]. |
|---------|---------------------------------------------------------------------------------------------------------------|
| Low body mass index | Parental history of hip fracture |
| Current smoking | ≥ 3 alcoholic drinks per day |
| Higher daily glucocorticoid dose | Higher cumulative glucocorticoid usage |
| Intravenous pulse glucocorticoid usage | Declining central bone mineral density measurement that exceeds the least significant change |
Fig. 2. Approach to premenopausal women and men age <50 years initiating or receiving glucocorticoid therapy [17].

† See section 3.2.1
In a study comparing alendronate, vitamin D and calcitriol, alendronate increased lumbar spine BMD by 5.9% over 2 years, compared to 0.5% and 0.7% loss on vitamin D and calcitriol respectively. There was no difference at the femoral neck [21]. In a prevention study comparing alendronate and alfacalcidol over 18 months, patients on alendronate maintained or improved their lumbar spine and femoral neck BMD compared to BMD loss in the alfacalcidol group [22]. IV zoledronate produced a better gain in lumbar spine and femoral neck BMD compared to oral risedronate over 1 year [23]. Over 3 years, teriparatide led to a better gain in lumbar spine and femoral neck BMD and reduced the incidence of new vertebral fractures compared to alendronate [24]. Alendronate and risedronate also reduced vertebral fractures in patients on GC therapy [25,26]. Overall, the recent Cochrane review supports the use of bisphosphonates to reduce the risk of vertebral fractures and the prevention and treatment of GC-induced bone loss [27].

In women of child-bearing age who may wish to conceive after stopping active osteoporosis medication, drugs which have a fast off-set of effect on bone turnover markers, such as denosumab [28], ibandronate [29], risedronate [30] or teriparatide [31], may be considered. (Grade C, Level IV).

Treatment should be continued for as long as the patient is on GC. Expert consensus recommends that therapy may be withdrawn in a subject on GC if BMD is close to normal and the patient is no longer at increased risk of fracture or when GC are stopped [32] (Grade C, Level IV). Once GC therapy is stopped, fracture risks decreased towards baseline values over the following 1 year [6] (Level III).

In conclusion, we hope that this guidance document will provide practical and relevant help to health care practitioners when making clinical decisions on managing their patients with GIO. This article is not meant to be a comprehensive review of all aspects of GIO, neither is it prescriptive. The key messages are to think of bone protection measures in all patients on GC, and, in patients at high risk of osteoporosis, bisphosphonates are the mainstay of treatment.

### Key points

- **Patients should be prescribed the lowest dose of GC for the shortest period of time that will give good disease control.**
- **Patients with a prevalent osteoporotic fracture should receive active osteoporosis medication.**
- **Patients who are on GC doses equivalent to prednisolone >5 mg daily should be assessed with BMD measurement and/or FRAX to assess future fracture risk and treatment options.**
- **Active osteoporosis therapy should be continued for the duration of GC therapy.**

---

**Table 2**

Grades of recommendation for preventive and therapeutic interventions in glucocorticoid-induced osteoporosis (GIO).

| Drug            | Primary Prevention | Secondary Prevention | Vertebral Fracture Reduction | References |
|-----------------|--------------------|----------------------|-------------------------------|------------|
| Alendronate     | A                  | A                    | A                             | [25,33]    |
| Alendronate     | A                  | A                    | ND                            | [34]       |
| Alfacalcidol    | A                  | A                    | ND                            | [35,36]    |
| Calcitriol      | A                  | ND                   | ND                            | [37]       |
| Calcium and vitamin D | ND | A                    | ND                            | [38]       |
| Denosumab       | ND                 | A                    | ND                            | [39,40]    |
| Hormone Therapy | ND                 | A                    | ND                            | [41]       |
| Ibandronate     | A                  | A                    | ND                            | [42]       |
| Pamidronate     | A                  | A                    | ND                            | [43,44]    |
| Raloxifene      | ND                 | A                    | ND                            | [45]       |
| Risedronate     | A                  | A                    | A                             | [26,46]    |
| Teriparatide    | ND                 | A                    | A                             | [24]       |
| Testosterone (in males) | ND | A                    | ND                            | [47]       |
| Zoledronate     | A                  | A                    | ND                            | [23]       |

**Primary Prevention**: Given within 3–4 months of initiation of glucocorticoid therapy.

**Secondary Prevention**: Treatment following an osteoporotic fracture or use of glucocorticoid for longer than 3–4 months.

ND: No benefit demonstrated/no data.

* These agents have studies showing efficacy in GIO but they do not have an indication from regulatory authorities for the treatment of GIO.

(> 7.5 mg daily), probabilities can be revised upward by about 15% [18].

### 3.2. Treatment options

#### 3.2.1. General measures

- **a)** Prescribing the lowest effective dose of GC for the shortest period of time for good disease control [17].
- **b)** The use of alternative route of administration [14] (e.g. inhaled GC in asthma)
- **c)** Consider the use of GC-sparing agents
- **d)** Modification of lifestyle - adequate calcium intake, adequate mobilisation, regular weight-bearing exercise, stopping smoking, avoiding excessive alcohol intake (<2 drinks per day) and prevention of falls [17] (Grade C, Level IV)

#### 3.2.2. Specific measures

In hypogonadal states, replacement therapy with sex steroids should be considered (Grade A, Level Ib).

All patients on GC should be supplemented with calcium and vitamin D (1000–1500 mg/day and 800 IU/day respectively) [19,20] (Grade A, Level Ia).

Drugs that have been shown to be effective in GIO are shown in Table 2. The management algorithm for the management of postmenopausal women and men over the age of 50 years on GC is shown in Fig. 1 and for premenopausal women and men under the age of 50 is shown in Fig. 2.

In patients on GC with osteoporotic fractures or confirmed osteoporosis on DXA, bisphosphonates are the first-line treatment (Grade A, Level Ib).
Conflict of interest

All the authors of this guidance have declared no conflicts of interest. The development of this guidance was fully funded by the Malaysian Osteoporosis Society.

Appendix 1.

Levels of Evidence and Grades of Recommendation

| Levels | Type of evidence |
|--------|------------------|
| Ia     | Evidence obtained from meta-analysis of randomised controlled trials (RCTs) |
| Ib     | Evidence obtained from at least one RCT |
| Iia    | Evidence obtained from at least one well designed controlled study without randomisation |
| Iib    | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| III    | Evidence obtained from well-designed non-experimental descriptive studies e.g. comparative studies, correlation studies, case-control studies |
| IV     | Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities, or both |

Grades of Recommendation

| Grades | Recommendation |
|--------|----------------|
| A (evidence levels Ia and Ib) | Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation |
| B (evidence levels Ila, Iib and III) | Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation |
| C (evidence level IV) | Required evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicated absence of directly applicable clinical studies of good quality |

Modified from the Scottish Intercollegiate Guidelines Network (SIGN) [13]

References

[1] van Staa TP, Cooper C, Abenhaim L, Begaud B, Zhang B, Leufkens HGM. Utilisation of oral corticosteroids in the United Kingdom. Q J Med 2000;93:105–11.
[2] Overman RA, Yeh J-Y, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res 2010;62:1515–26.
[3] Weiss RJ, Wick MC, Ackermann PW, Montgomery SM. Increased fracture risk in patients with rheumatic disorders and other inflammatory diseases — a case-control study with 53,108 patients with fracture. J Rheumatol 2010;37:2247–50.
[4] van Staa TP, Geusens P, Bijlsma JWJ, Leufkens HGM, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:3104–12.
[5] van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002;13:777–87.
[6] van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
[7] van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 2003;48:3224–9.
[8] National Osteoporosis Foundation. Clinician’s guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2013. http://enr.tums.ac.ir/upfiles/158936855.pdf.
[9] Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. Lancet 2000;355:1399–403.
[10] Gonnelli S, Caffarelli C, Maggi S, Guglielmi G, Siviero P, Rossi S, et al. Effect of inhaled glucocorticoids and beta(2) agonists on vertebral fracture risk in COPD patients: the EOLE study. Calcif Tissue Int 2010;87:137–43.
[11] Hubbard RB, Smith CJ, Smeeth L, Harrison TW, Tattersfield AE. Inhaled corticosteroids and hip fracture: a population-based case-control study. Am J Respir Crit Care Med 2002;166:1563–6.
[12] Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. West J Med 1999;170:348–51.
[13] Harbour R, Miller J, for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323:344–6.
[14] Eastell R, Reid DM, Compton I, Cooper C, Fogelman I, Francis RM, et al. A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. J Intern Med 1998;244:271–92.
[15] Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton III LJ, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004;19:893–9.
[16] FRAX®: Fracture Risk Assessment Tool [Internet]. UK: Centre for Metabolic Bone Diseases, University of Sheffield, [cited 2017 Jan 02]. Available from: http://www.shef.ac.uk/FRAX/.
[17] Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 2010;62:1515–26.
[18] Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011;22:809–16.
[19] Amin S, LaValley MP, Simms RW, Felson DT. The role of vitamin D in corticosteroid osteoporosis. A meta-analytic approach. Arthritis Rheum 1999;42:1740–51.
[20] Homik J, Suarez-Almazor ME, Shea B, Cranney A, Wells G, Tugwell P. Calcium and vitamin D for corticosteroid-induced osteoporosis. Cochrane Database Syst Rev 2000;2:CD000952.
[21] Sambrook PN, Kotowicz M, Nash P, Styles CB, Naganathan V, Henderson-Briffa KN, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium and alendronate plus calcium. J Bone Miner Res 2003;18:919–24.
[22] de Nijs RN, Jacobs JW, Lems WF, Laan RF, Algra A, Huisman AM, et al. Alendronate or alfalcacidol in glucocorticoid-induced osteoporosis. N Engl J Med 2006;355:675–84.
[23] Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledron acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy randomised controlled trial. Lancet 2009;373:1253–63.
[24] Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis. Arthritis Rheum 2009;60:3346–55.
[25] Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2001;44:202–11.
[26] Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000;67:277–85.

[27] Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev 2016 Oct 5;10:CD001347.

[28] Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab 2011;96:972–80.

[29] Ravn P, Christensen JO, Baumann M, Clemmesen B. Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: prediction of bone mass changes during treatment. Bone 1998;22:559–64.

[30] Eastell R, Hannon RA, Wenderoth D, Rodriguez-Moreno J, Sawicki A. Effect of stopping risedronate after long-term treatment on bone turnover. J Clin Endocrinol Metab 2011;96:3367–73.

[31] Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparadine in postmenopausal women with osteoporosis. Arch Intern Med 2004;164:2024–30.

[32] Rizzoli R, Adachi JD, Cooper C, Dere W, Devogelaer JP, Diez-Perez A, et al. Management of glucocorticoid-induced osteoporosis. Calcif Tissue Int 2012;91:225–43.

[33] Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292–9.

[34] Stoch SA, Saag KG, Greenwald M, Sebba AI, Cohen S, Verbruggen N, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol 2009;36:1705–14.

[35] Reginster JY, Kuntz D, Verdec D, Wouters M, Guillemin L, Menkès CJ, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporos Int 1999;9:75–81.

[36] Ringe JD, Cöster A, Meng T, Schacht E, Umbach R. Treatment of glucocorticoid-induced osteoporosis with alfacalcidol/calcium versus vitamin D/calcium. Calcif Tissue Int 1999;65:337–40.

[37] Sambrook P, Birmingham J, Kelly P, Kemppler S, Nguyen T, Pocock N, et al. Prevention of corticosteroid osteoporosis—a comparison of calcium, calcitriol, and calcitonin. N Engl J Med 1993;328:1747–52.

[38] Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroid in patients with rheumatoid arthritis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996;125:961–8.

[39] Dore RK, Cohen SB, Lane NE, Palmer W, Shergy W, Zhou L, et al. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. Ann Rheum Dis 2010;69:872–5.

[40] Mok CC, Ho LY, Ma KM. Switching of oral bisphosphonates to denosumab in chronic glucocorticoid users: a 12-month randomized controlled trial. Bone 2015;75:222–8.

[41] Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis Rheum 1994;37:1499–505.

[42] Hakala M, Kröger H, Valleeala H, Hienonen-Kemppa T, Lehtonen-Veromaa M, Heikkinen J, et al. Once-monthly oral ibandronate provides significant improvement in bone mineral density in postmenopausal women treated with glucocorticoids for inflammatory rheumatic diseases: a 12-month, randomized, double-blind, placebo-controlled trial. Scand J Rheumatol 2012;41:260–6.

[43] Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. J Bone Miner Res 2001;16:104–12.

[44] Krieg MA, Seydoux C, Sandini L, Goy JJ, Berguer DG, Thiébaut D, et al. Intravenous pamidronate as treatment of osteoporosis after heart transplantation: a prospective study. Osteoporos Int 2001;12:112–6.

[45] Mok CC, Ying KY, To CH, Ho LY, Yu KL, Lee HK, et al.Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial. Ann Rheum Dis 2011;70:778–84.

[46] Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve month, multi-centre, randomized, double-blinded, placebo-controlled, parallel-group study. Arthritis Rheum 1999;42:2309–18.

[47] Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy in glucocorticoid-treated men. Arch Intern Med 1996;156:1173–7.