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CONSENSUS STATEMENT

Recommendations for the registration of agents for prevention and treatment of glucocorticoid-induced osteoporosis: an update from the Group for the Respect of Ethics and Excellence in Science

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Oral glucocorticoid therapy is widely used for the treatment of a variety of diseases. Approximately 1% of the population is prescribed oral glucocorticoids, and in the elderly this prevalence rises to 2.5% [1]. The association between glucocorticoid therapy and osteoporosis is well documented and exhibits some characteristic features [2]. Bone loss is particularly rapid in the first few months after initiation of therapy, with a slower rate of loss subsequently [3]. Fracture risk also increases rapidly during the early months of therapy and declines after its cessation [4, 5]. Both cortical and cancellous bone are affected, and there is some reversibility of bone loss after cessation or reduction of therapy [3, 6]. Although the severity of osteoporosis is related to the dose and

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duration of glucocorticoid therapy, some increase in fracture risk is seen even at daily doses of ≤7.5 mg daily for 3–6 months [4, 5]. Finally, the effect of glucocorticoids on bone fragility is, to some extent, independent of bone mineral density, fractures occurring at a higher bone mineral density (BMD) threshold than in postmenopausal osteoporosis (PMO) [7–9].

Glucocorticoid-induced osteoporosis (GIOP) and PMO share a number of characteristics with respect to the cellular pathophysiology of bone loss. Increased bone turnover occurs in both conditions, but differs in its time course. In GIOP, an early and transient increase in bone turnover occurs against a background of low bone turnover with reduced bone formation at both tissue and cellular levels [10–13]. The early increase in bone turnover in GIOP is likely to be a major contributor to bone loss and increased fracture risk within the first few months of initiating therapy and is therefore an important therapeutic target. In PMO, increased bone turnover is consistently observed over time. Both GIOP and PMO are associated with a reduction in bone formation at the cellular level, this effect being quantitatively greater in GIOP than PMO and associated with a reduction in bone formation at the tissue level. Similar effects on cancellous bone microarchitecture have also been reported in the two conditions, depending on the dose of glucocorticoids used [10].

Treatment studies in GIOP are complicated by the heterogeneity of the population at risk in terms of age, gender, underlying disease, co-morbidities and co-medications, and the dose and duration of glucocorticoid therapy. The majority of studies have been short-term (one-year studies) with BMD, not fracture, as the primary end-point. Traditionally, such studies have been regarded as sufficient to obtain approval of an agent for the prevention and treatment of GIOP if that agent has established anti-fracture efficacy in PMO. However, the majority of those participating in these studies have been postmenopausal women and the evidence-base for efficacy in glucocorticoid-treated men and premenopausal women is therefore weak.

Recommendations for the registration of agents for the prevention and treatment of GIOP were produced by the Group for the Respect of Ethics and Excellence in Science (GREES) in 1996 [14] and subsequently updated in 2005 [15]. The 2005 update mainly addressed the design of clinical studies in glucocorticoid-treated postmenopausal women and concluded that for agents with proven efficacy in PMO a placebo-controlled trial with lumbar spine BMD at 1 year as the primary endpoint was required. The aim of the update described in this paper is to consider separately appropriate recommendations for the registration of agents for use in GIOP in postmenopausal women, men and premenopausal women. At present etidronate, alendronate, risedronate and teriparatide have approval for the prevention and treatment of glucocorticoid-induced osteoporosis in Europe. In the case of risedronate (the only compound that was centrally registered) this is limited to postmenopausal women.

Preclinical, phase I and phase II studies

In line with previous recommendations [15], preclinical and phase 1 and phase II studies with agents approved for PMO do not need to be repeated for a new indication for that agent in GIOP. However, if agents not approved for PMO are being developed for GIOP, the preclinical program required

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for PMO and the traditional phase I and phase II studies are required prior to phase III studies.

Terminology and thresholds for treatment

In the context of GIOP, the terms prevention and treatment are used to differentiate intervention at the start of glucocorticoid therapy and intervention after at least 3 months of glucocorticoid therapy. Whilst this distinction is important in clinical practice because of the early increase in fracture risk after initiation of glucocorticoid therapy, the group recommends that it is no longer necessary for regulatory purposes and that the need for intervention at any point in time should be based on absolute fracture risk.

Phase III studies

General considerations

Phase III studies should aim to include patients with a broad variety of underlying glucocorticoid-treated illnesses. They may include both patients who are starting oral glucocorticoid therapy and those already established on treatment. For the purposes of these recommendations, patients undergoing transplantation procedures are not included because of the heterogeneity of the underlying diseases and the use of other bone active medications. The majority of patients should be on a previous or projected dose of at least 5 mg daily of prednisolone (or equivalent) and all those enrolled should be given calcium and vitamin D supplementation (500 mg to 1 g calcium and 400–800 IU vitamin D daily). Studies should allow for separate estimation of efficacy in females and males. This could be done either in separate trials or in mixed populations by stratification, with provision in the planned statistical analysis for separate examination of treatment effects in men and women and the effect of key factors such as underlying disease, menopausal status and concurrent medication. Although placebo-controlled studies with fracture as the primary end-point would provide the optimal trial design, these are not considered ethically justifiable in view of the high fracture risk in glucocorticoid-treated patients [16–18] and the existence of effective treatments.

Consideration should also be given to obtaining an adequate safety database in phase III studies. Because of the high co-morbidity and co-medication associated with glucocorticoid-treated illnesses, adverse effects of agents may be greater in their frequency and severity than in non-glucocorticoid treated populations. In addition, because of the ability of some drugs (e.g. bisphosphonates) to cross the placenta, there may be specific safety concerns in premenopausal women.

Postmenopausal women

For agents that have been granted marketing authorisation for the treatment of PMO in women at increased risk of fracture a bridging study based on BMD is recommended in previous guidance for GIOP [15]. The design should be a non-inferiority study with lumbar spine BMD at one year as the primary end-point. Approved and established drug therapies for GIOP should be used as the active comparator.

The approved indications for GIOP and PMO should remain separate and for the former should be worded as “for glucocorticoid-treated postmenopausal women at increased risk of fracture”. Absolute fracture risk in glucocorticoid-treated postmenopausal women is generally higher than in non-glucocorticoid treated postmenopausal women with osteoporosis, despite higher baseline BMD values in the former.

Men

At any given age, the fracture probability in men is lower than that in women, regardless of whether they are receiving glucocorticoid therapy. Agents currently approved in Europe for the treatment of osteoporosis in men at increased risk of fracture are alendronate [19], risedronate [20] and teriparatide [21]. Approval for these agents was based on BMD bridging studies; hence the evidence base for fracture reduction with these treatments in non-glucocorticoid treated men is less robust than that for PMO.

As with postmenopausal women, the approved indications for GIOP and male osteoporosis should remain separate, and the latter should be worded as for glucocorticoid-treated men at increased risk of fracture. For agents that are already approved for the treatment of osteoporosis in men at increased risk of fracture, a non-inferiority study with lumbar spine BMD at one year as the primary end-point should be performed using an approved active comparator, comparing the effect in glucocorticoid-treated and non-glucocorticoid-treated men.

For agents that are not approved for the treatment of osteoporosis in men at increased risk of fracture but are approved for treatment of PMO, two bridging studies are required, both non-inferiority studies with lumbar spine BMD at one year as the primary end-point. The first bridging study should compare the effect of the agent in glucocorticoid-treated and non-glucocorticoid-treated postmenopausal women, followed by a second bridging study comparing the effect between glucocorticoid-treated postmenopausal women and glucocorticoid-treated men.

For agents that do not have approval for the treatment of either osteoporosis in men or postmenopausal women at increased risk of fracture, the only option is a placebo-

controlled double-blind randomised trial; with fracture reduction as the primary end-point.

Premenopausal women

Although fractures may occur in premenopausal women treated with glucocorticoids, the absolute risk is very low. Furthermore, the relationship between BMD and fracture risk in premenopausal women has not been established, regardless of whether they are treated with glucocorticoids. Finally, there are specific safety concerns in premenopausal women related to the ability of some interventions to cross the placenta. For these reasons the group agreed that at the present time BMD bridging studies in premenopausal women would not provide adequate evidence for anti-fracture efficacy. However, further research is recommended to identify risk factors for fracture in this population.

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