



EDUCATIONAL OBJECTIVE: Readers will assess the risk of fractures in their patients receiving glucocorticoid therapy

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Recent recommendations on steroid-induced osteoporosis: More targeted, but more complicated

ABSTRACT

The latest recommendations for preventing and treating glucocorticoid-induced osteoporosis, published by the American College of Rheumatology (ACR) in 2010, incorporate developments that occurred since the release of its 2001 guidelines, such as new drugs and the World Health Organization's Fracture Risk Assessment Tool, or FRAX. They outline a more targeted approach but have the possible disadvantage of being more complicated and therefore harder to use.

KEY POINTS

The risk of fracture should be assessed at the start of glucocorticoid therapy.

Factors that affect the decision to prescribe osteoporosis drugs include the patient's risk of fractures as assessed with FRAX (www.shef.ac.uk/FRAX), the dose of glucocorticoid, and the projected duration of treatment.

Since FRAX treats glucocorticoid use simply as a yes-or-no question, it likely underestimates the fracture risk in current users and at high doses. The estimate of risk should be adjusted upward in these situations.

WHENEVER A PATIENT begins treatment with a glucocorticoid drug, we need to think about bone loss.

The American College of Rheumatology (ACR) issued recommendations for preventing and treating glucocorticoid-induced osteoporosis in 2010.¹ Compared with its previous guidelines,² the new ones are more tailored and nuanced but may be more difficult for physicians to follow. The guidelines call for assessing fracture risk using the computer-based Fracture Risk Assessment Tool, or FRAX (www.shef.ac.uk/FRAX), developed by the World Health Organization (WHO). For those without a computer or ready access to the Web, an application of FRAX is available for download on smartphones.

In this article, my purpose is to review the new recommendations and to offer my perspective, which does not necessarily reflect the opinions of the ACR.

DESPITE EVIDENCE, MANY PATIENTS RECEIVE NO INTERVENTION

Use of glucocorticoids is the most common cause of secondary osteoporosis. During the first 6 to 12 months of use, these drugs can cause a rapid loss of bone mass due to increased bone resorption; with continued use, they cause a slower but steady decline in bone mass due to reduced bone formation.³ Epidemiologic studies have found that the risk of fractures increases with dose, starting with doses as low as 2.5 mg per day of prednisone or its equivalent.⁴

*Dr. Deal has disclosed that he has been a consultant and speaker for Amgen and Lilly.

Despite the risk of fractures with steroids and the efficacy of available agents in preventing bone loss and fracture, many patients do not receive any intervention

Numerous clinical trials have evaluated the effect of bisphosphonates and teriparatide (Forteo) on bone mass and fracture risk in patients on glucocorticoid therapy. The bisphosphonates alendronate (Fosamax) and risedronate (Actonel) have both been shown to increase bone mass and reduce vertebral fracture risk in glucocorticoid recipients.⁵⁻⁸ Zoledronic acid (Reclast), a parenteral bisphosphonate given in one annual dose, was shown to increase bone mass more than oral risedronate taken daily,⁹ and teriparatide, a formulation of parathyroid hormone, was better than alendronate.¹⁰

However, despite the known risk of fractures with glucocorticoid use and the demonstrated efficacy of available agents in preventing bone loss and fracture, many patients do not receive any intervention.^{11,12}

■ WHAT HAS HAPPENED SINCE 2001?

In the interval since 2001, several guidelines for managing glucocorticoid-induced osteoporosis have been published in other countries.¹³⁻¹⁷ Broadly speaking, they recommend starting preventive drug therapy for patients at risk of fracture at the same time glucocorticoid drugs are started if the patient is expected to take glucocorticoids for more than 3 to 6 months in doses higher than 5 to 7.5 mg of prednisone or its equivalent daily.

Recommendations for patients who have been on glucocorticoids for longer than 3 to 6 months at initial evaluation have been based largely on T scores derived from dual-energy x-ray absorptiometry (DXA). Thresholds for initiating therapy have varied: the ACR in 2001 recommended preventive treatment if the T score is lower than -1.0, whereas British guidelines said -1.5 and Dutch guidelines said -2.5.

In the United States, since 2001 when the ACR published its last guidelines,² zoledronic acid and teriparatide have been approved for use in glucocorticoid-induced osteoporosis. In addition, guideline-development methodology has evolved and now is more scientifically rigorous. Finally, a risk-assessment tool has been developed that enables a more tailored approach (see below).

FRAX (www.shef.ac.uk/FRAX)

FRAX is a tool developed by the WHO to calculate the risk of fracture. If you go to the FRAX Web site and enter the required clinical information (race, age, sex, weight, height, previous fracture, family history of a fractured hip in a parent, current smoking, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, consumption of three or more units of alcohol per day, and bone mineral density of the femoral neck), it will tell you the patient's 10-year absolute (not relative) risk of major osteoporotic fracture and of hip fracture.

Since FRAX was unveiled in 2008, calculation of absolute fracture risk has become the standard method for making treatment decisions in patients with low bone mass who have not yet received any fracture-preventing treatment.¹⁸ The use of clinical risk factors in FRAX increases its ability to predict risk over and above the use of bone density by itself. And glucocorticoids are one of the clinical risk factors in FRAX.

But in which patients is treatment with a bisphosphonate or teriparatide cost-effective?

Thresholds for cost-effectiveness have been developed on the basis of economic assumptions that are country-specific. In the United States, the National Osteoporosis Foundation recommends drug therapy if the 10-year absolute risk of a major osteoporotic fracture of the hip, spine (clinical, not radiographic), wrist, or humerus is greater than 20% or if the risk of a hip fracture is greater than 3%.¹⁹

At equivalent bone densities, women taking glucocorticoids are at considerably higher risk of fracture than nonusers.²⁰ For example, consider a 65-year-old white woman, weight 59 kg, height 163 cm, no previous fractures, no parent with a fractured hip, no current smoking, no rheumatoid arthritis, no secondary osteoporosis, no excessive alcohol use, and a T score of -2.2 in the femoral neck. (Try this on the FRAX Web site.) If she does not use glucocorticoids, her 10-year risk of hip fracture is 2.0%; using glucocorticoids increases the risk to 3.6%. This is higher than the 3% National Osteoporosis Foundation guideline; thus, treatment would be recommended.

Also using FRAX, a 55-year-old white woman with a T score of -1.8 and on glucocorticoid therapy has a 67% higher risk of ma-

for osteoporotic fracture and an 80% higher risk of hip fracture.

For a third example, a white woman age 60, weight 70 kg, height 168 cm, negative for all the other risk factors but with a T score of -2.1 and on glucocorticoids has a calculated 10-year fracture risk of 2.1%, which is below the National Osteoporosis Foundation treatment threshold. However, most clinicians would probably recommend treatment for her, depending on the anticipated dose and duration of glucocorticoid therapy.

A caveat. In FRAX, glucocorticoid therapy is a categorical variable—a yes-or-no question—and yes is defined as having ever used a glucocorticoid in a dose greater than 5 mg for more than 3 months. Therefore, according to FRAX, a patient who took 5 mg of prednisone for 3 months 5 years ago has the same fracture risk as a patient on 60 mg of prednisone after a diagnosis of temporal arteritis. For this reason, the FRAX tool is likely to underestimate fracture risk, especially in patients currently taking glucocorticoids and those on higher doses of these drugs.

Kanis et al used the General Practice Research Database to adjust the fracture risk for glucocorticoid use in FRAX.²¹ At doses higher than 7.5 mg, the fracture risk had to be revised upward by 10% to 25% depending on the fracture site (hip vs any major osteoporotic fracture) and age (greater at age 40 than at age 90).

The underestimation of fracture risk led the ACR Expert Advisory Panel to create risk strata for major osteoporotic fractures, ie, low ($< 10\%$ risk per 10 years), medium (10% – 20%), and high ($> 20\%$) and uses these cut points to make treatment recommendations.

■ HOW THE 2010 GUIDELINES WERE DEVELOPED

Whereas the 2001 recommendations were based on a more informal consensus approach, the 2010 recommendations use a more scientifically rigorous methodology for guideline development, the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method. The RAND/UCLA method combines the best available scientific evidence with expert opinion to develop practice guidelines.

TABLE 1

Lifestyle modifications and assessment of patients starting glucocorticoids for 3 months or more

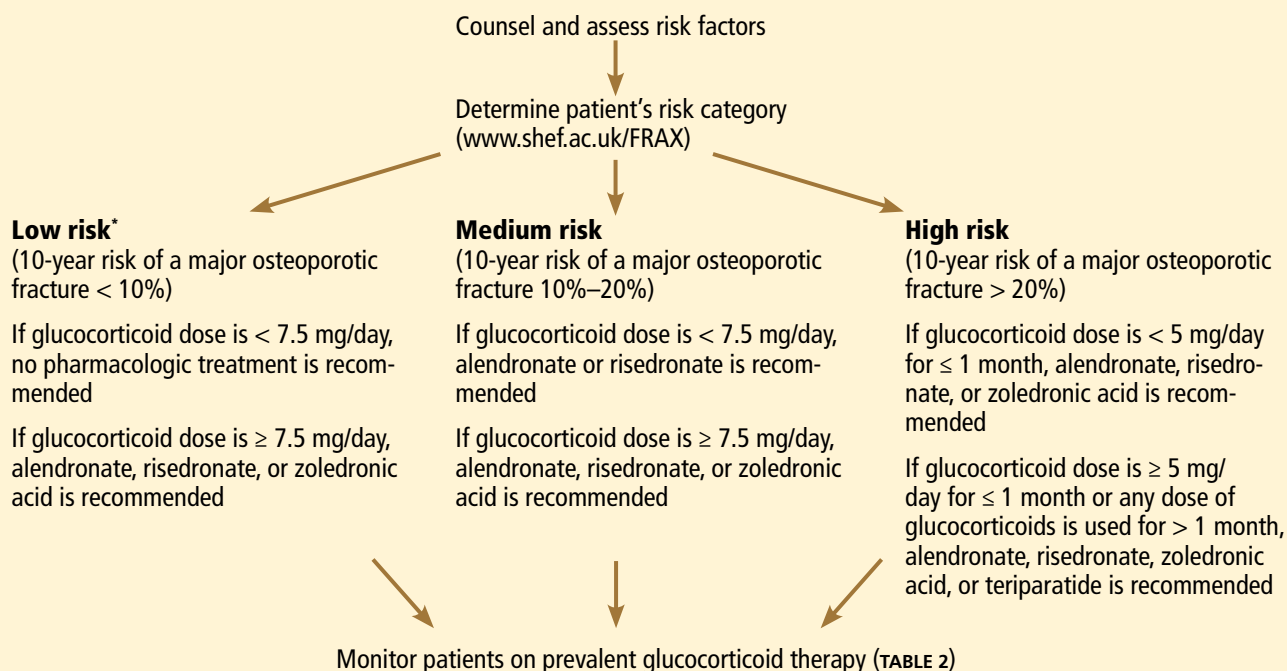
Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (> 2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Assessment of risk of falling	C
Baseline dual-energy x-ray absorptiometry (DXA)	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment (by DXA) for those initiating or currently receiving prednisone ≥ 5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) of 1,200–1,500 mg daily	A
Vitamin D supplementation*	A

*Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids rather than a duration of at least 3 months.

GROSSMAN JM, GORDON R, RANGANATH VK, ET AL. AMERICAN COLLEGE OF RHEUMATOLOGY 2010 RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS. ARTHRITIS CARE RES (HOBOKEN) 2010; 62:1515–1526.

In drawing up the 2010 recommendations the ACR used three panels of experts. The Core Executive Panel conducted a systematic review of controlled clinical trials of therapies currently approved for treating glucocorticoid-induced osteoporosis in the United States, Canada, or the European Union. They found 53 articles meeting their inclusion criteria; an evidence report was

Approach to postmenopausal women and men age 50 years and older starting or receiving glucocorticoid therapy



*For patients at low or medium risk, recommendations are for an anticipated or prevalent duration of ≥ 3 months of glucocorticoids.

FIGURE 1

produced that informed the development of the recommendations. This evidence report and guideline development process is available at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The Expert Advisory Panel framed the recommendations, and the Task Force Panel voted on them. The Core Executive Panel and Expert Advisory Panel constructed 48 patient-specific clinical scenarios using four variables: sex, age, race/ethnicity, and femoral neck T scores.

The members of the Task Force Panel were asked to use the evidence report and their expert judgment to vote on and rate the appropriateness of using a specific therapy in the context of each scenario on a 9-point Likert scale (1 = appropriate; 9 = not appropriate). Agreement occurred when 7 or more of the 10 panel members rated a scenario 1, 2, or 3. Disagreements were defined as 3 or more of the 10 members rating the scenario between 4 and 9 while the other members rated it lower.

Disagreements in voting were discussed in

an attempt to achieve consensus, and a second vote was conducted which determined the final recommendations. If disagreement remained after the vote, no recommendation was made.

No attempt was made to assign priority of one drug over another when multiple drugs were deemed appropriate, although the final recommendations did differentiate drugs based on patient categories.

START WITH COUNSELING, ASSESSMENT

For patients starting or already on glucocorticoid therapy that is expected to last at least 3 months, the first step is to counsel them on lifestyle modifications (TABLE 1) and to assess their risk factors (FIGURE 1). Recommendations for monitoring patients receiving glucocorticoid therapy for at least 3 months are presented in TABLE 2.

These recommendations are based on literature review, and the strength of evidence is graded:

- Grade A—derived from multiple randomized controlled trials or a meta-analysis
- Grade B—derived from a single randomized controlled trial or nonrandomized study
- Grade C—derived from consensus, expert opinion, or case series.

This system is the same one used by the American College of Cardiology and is based on clinical trial data.²²

Recommendations for calcium intake and vitamin D supplementation were graded A; all other recommendations were graded C (TABLES 1 AND 2). It is important to note that practices that receive a grade of C may still be accepted as standard of care, such as fall assessment and smoking cessation.

■ FOR POSTMENOPAUSAL WOMEN AND FOR MEN AGE 50 AND OLDER

FRAX low-risk group

Recall that “low risk” based on the new ACR guidelines means that the 10-year absolute risk of a major osteoporotic fracture, as calculated with FRAX, is less than 10%.

- If glucocorticoid use is expected to last or has already lasted at least 3 months and the dose is less than 7.5 mg/day, no pharmacologic treatment is recommended.
- If glucocorticoid use is expected to last or has already lasted at least 3 months and the dose is 7.5 mg/day or higher, alendronate, risedronate, or zoledronic acid is recommended.

Comment. These are the most straightforward of the recommendations. All three bisphosphonates are recommended as treatment options if the glucocorticoid dose is at least 7.5 mg/day and the duration at least 3 months. Ibandronate (Boniva) was not included because it has no data from clinical trials.

FRAX medium-risk group

“Medium risk” means that the 10-year absolute fracture risk of major osteoporotic fractures is 10% to 20%.

- If glucocorticoid use is anticipated to last or has lasted at least 3 months and the dose is less than 7.5 mg/day, alendronate or risedronate is recommended.
- If glucocorticoid use is anticipated to last or has lasted at least 3 months and the dose is 7.5 mg/day or higher, alendronate,

TABLE 2

Recommendations for monitoring for patients receiving glucocorticoids for at least 3 months

Recommendation	Level of evidence
Consider serial bone mineral density testing	C
Consider annual serum 25-hydroxyvitamin D measurement	C
Annual height measurement	C
Assessment of incident fragility fracture	C
Assessment of medication compliance	C

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risedronate, or zoledronic acid is recommended.

Comment. Treatment is recommended at all glucocorticoid doses for patients in the medium-risk category if the duration of glucocorticoid treatment is at least 3 months, with one difference: zoledronic acid is recommended only if the glucocorticoid dose is 7.5 mg/day or higher. This inconsistency persisted after a second round of voting by the Task Force Panel.

FRAX high-risk group

In this group, the 10-year risk of major osteoporotic fractures is higher than 20%.

- If the glucocorticoid dose is less than 5 mg/day for up to 1 month, alendronate, risedronate, or zoledronic acid is recommended.
- If the dose is 5 mg/day or more for up to 1 month, or any dose for more than 1 month, alendronate, risedronate, zoledronic acid or teriparatide is recommended.

Comment. Based on current National Osteoporosis Foundation guidelines, all patients with a 10-year risk greater than 20% are recommended for treatment for any duration and dose of glucocorticoid use. However, teriparatide is recommended only if the duration of glucocorticoid therapy is more than 1 month.

At equivalent bone densities, women taking glucocorticoids are at considerably higher risk of fracture than nonusers

■ FOR PREMENOPAUSAL WOMEN AND FOR MEN YOUNGER THAN AGE 50

Use of FRAX is not appropriate in premenopausal women or in men younger than 50 years.

Younger patients with no prevalent fracture

For men younger than 50 and premenopausal women who have not had a previous fracture, data were considered inadequate to make a recommendation, and no votes were taken.

Prevalent fracture in premenopausal women of nonchildbearing potential

In premenopausal women of nonchildbearing potential who have had a fracture:

- If the glucocorticoid duration is 1 to 3 months and the dose is 5 mg/day or higher, alendronate or risedronate is recommended.
- If the duration is 1 to 3 months and the dose is 7.5 mg/day or higher, alendronate, risedronate, or zoledronic acid is recommended.
- If the duration is more than 3 months, alendronate, risedronate, zoledronic acid, or teriparatide is recommended.

Comment. Treatment is recommended with any of the four medications in patients with a fracture and treated with glucocorticoids for more than 3 months. For shorter-duration glucocorticoid use (1–3 months) at 5 mg/day or higher, only alendronate and risedronate are recommended. If the dose is 7.5 mg/day or higher, any bisphosphonate is recommended. Zoledronic acid was consistently differentiated by the expert panel on the basis of dose and duration of glucocorticoid use, in view of its 1-year duration of effect after one dose.

Prevalent fracture in women of childbearing potential

- If the glucocorticoid duration is 1 to 3 months, there was no consensus (ie, voting disagreements could not be resolved).
- If the glucocorticoid duration is more than 3 months and the dose is 7.5 mg/day or more, alendronate, risedronate, or teriparatide is recommended.
- If the glucocorticoid duration is more than 3 months and the dose is less than 7.5 mg/day, there was no consensus.

Comment. Childbearing potential creates further complexities because of concern about fetal toxicity with bisphosphonates. For short-term glucocorticoid therapy at any dose and for therapy longer than 3 months at less than 7.5 mg, no consensus could be reached. For therapy longer than 3 months and with 7.5 mg/day or higher, treatment is recommended but not with zoledronic acid, based on the long half-life of the drug and concern for fetal toxicity.

Additional risk stratification

The panel recommended that if the following were present, a shift to a higher fracture risk category should be considered (low to medium, or medium to high):

- High daily dose of glucocorticoid
- High cumulative glucocorticoid dose
- Declining bone mineral density on serial DXA.

These are known risk factors that increase fracture risk but would not affect fracture risk in the FRAX model.

■ WHAT IS NEW IN THE 2010 RECOMMENDATIONS?

Recommendations for counseling now include fall risk assessment, height measurement, 25-hydroxyvitamin D measurement, and evaluation of patients for prevalent and incident fractures using vertebral fracture assessment by DXA or radiographic imaging of the spine.

Recommended drugs now include teriparatide and zoledronic acid, while estrogen and testosterone are no longer recommended as therapies for glucocorticoid-induced osteoporosis. Ibandronate is not included, since there have been no randomized controlled trials of this bisphosphonate in glucocorticoid-induced osteoporosis.

Recommendations for treatment in 2001 were based on T scores alone, while the 2010 recommendations use an assessment of absolute fracture risk based on FRAX for postmenopausal women and for men age 50 and older.

A clinician's guide that summarizes the ACR recommendations is available at www.rheumatology.org/practice/clinical/guidelines/.

FRAX is likely to underestimate fracture risk, especially in patients currently on glucocorticoids and those on higher doses

RECOMMENDATIONS DO NOT REPLACE CLINICAL JUDGMENT

Although the 2010 recommendations were more rigorous in their development process than those of 2001, they have limitations and they should not replace clinical judgment. Rather, they are intended to provide an evidence-based approach to guide clinicians in making treatment choices in patients on glucocorticoid therapy.

CONSIDERING ABSOLUTE FRACTURE RISK IN TREATMENT DECISIONS

The 2001 ACR guidelines recommended fracture-preventing treatment in all patients starting glucocorticoid therapy at more than 5 mg/day if the planned duration of treatment was at least 3 months, and in patients on long-term glucocorticoid therapy if the T score was less than -1.0 . While these guidelines were simple and easy to use, they were not specific enough to provide useful guidance in specific scenarios.

A model of absolute fracture risk was not available in 2001. A 55-year old white woman with a T score of -1.1 who smoked, who had been using 5 mg of prednisone for the last 12 months, and who had stable bone mass on serial DXA scans would have been recommended for treatment based on the 2001 recommendations. If this patient's FRAX-calculated 10-year absolute risk of a major osteoporotic fracture is less than 10%, that would be well below the National Osteoporosis Foundation's cost-effective treatment threshold of 20%. The new guidelines suggest no treatment is needed, since the risk category is low and the dose is less than 7.5 mg. However, if on serial DXA this patient had a significant decline in bone mass, the guidelines suggest shifting the patient to a higher risk category, ie, from low to medium risk, which would result in a recommendation in favor of treatment.

The 2010 recommendations are not as simple to use as those from 2001. They encourage using FRAX to calculate fracture risk; thus, knowledge of the strengths and limitations of FRAX is required. Access to the internet in the examination room or use of the FRAX tool on a smartphone as well as will-

ingness to spend a minute to calculate fracture risk are needed. For those who cannot or choose not to use the FRAX tool, the ACR publication provides tables for patient risk assessment based on age and T score. However, the tables would have to be readily available in the clinic, which may not be practical.

The 2010 recommendation provide a more nuanced approach to treatment in patients on glucocorticoid therapy and are likely to change treatment decisions based on their use, just as FRAX has altered treatment decisions in patients with primary osteoporosis.²³

FRAX has limitations

FRAX underestimates the effect of glucocorticoids on fracture risk because steroid use is a yes-or-no question and its weight represents the average risk in a population that has ever used steroids, most of whom were using doses between 2.5 and 7.5 mg.

The WHO recognized this limitation and suggested an upward adjustment of risk for patients on 7.5 mg or more, ranging from 10% to 25%.²¹ For patients on high doses of steroids, this adjustment is still likely to result in underestimation of fracture risk and undertreatment of glucocorticoid-treated patients.

The 2010 recommendations adjust for this limitation, recommending treatment in the low-risk and medium-risk categories if the glucocorticoid dose is 7.5 mg or higher. If a patient is using high daily doses of steroids or has a declining bone density, the 2010 recommendations suggest increasing the risk category from low to medium or medium to high.

FRAX risk factors are dichotomous (yes/no) and are not adjusted for dose effects such as multiple fractures (vs a single fracture), heavy smoking (vs light smoking), heavy alcohol use (6 units per day vs 3 units), or severe rheumatoid arthritis (vs mild disease). Family history of osteoporosis in the FRAX is limited to parents with a hip fracture—vertebral fractures in a family member do not count.

Since FRAX uses the bone mineral density in the hip, it underestimates fracture risk in patients with low spine density but normal hip density. It may also underestimate fracture risk in patients with declining bone mass; the 2010 recommendations suggest the clinician should increase the risk category in this situation.

Practices that receive a grade of C may still be accepted as standard of care, such as fall assessment and smoking cessation

LIMITATIONS OF THE GUIDELINES

The 2010 recommendations do not include several important groups in which steroids are used, including transplant recipients, children, and patients on inhaled corticosteroids. The panel thought that there were insufficient data to make recommendations for these populations, as well as for premenopausal women and men younger than 50 years who did not have a prevalent fracture. The absence of a recommendation in these situations should not be considered a recommendation for no treatment; it is an acknowledgment of a lack of evidence, a lack of consensus among experts, and the need for additional clinical trials.

For premenopausal women and men under age 50 with a fracture, the recommendations are complicated and not intuitive. Zoledronic acid is not recommended for women of non-childbearing potential with a glucocorticoid duration of 1 to 3 months unless the steroid dose is at least 7.5 mg. This recommendation was based on panel voting and consensus that giving zoledronic acid, a medication with a 1-year duration of effect, in a patient on steroids for only 1 to 3 months was not warranted.

Teriparatide was recommended only if glucocorticoids are used for at least 3 months, although anyone who already has a fracture might be considered at high enough risk to warrant anabolic therapy regardless of steroid use or duration.

Zoledronic acid was excluded in women of childbearing potential, based on panel voting and consensus that drugs given in smaller amounts over 1 year might be less harmful to a fetus than one with a longer half-life given in a larger bolus once a year.

The panel could reach no consensus on women of childbearing potential with a prevalent fracture who were using less than 7.5

mg/day of glucocorticoids. A lack of consensus was the result of insufficient data to make evidence-based decisions and a disagreement among experts on the correct treatment.

The guidelines do not address the duration of treatment with bisphosphonates, a topic of importance because of concern for the potential long-term side effects of these medications.

THE BOTTOM LINE

The 2010 recommendations add a degree of complexity, with different medications recommended on the basis of glucocorticoid dose and duration as well as patient age, menopausal status, and childbearing potential. Guideline developers and clinicians face a difficult trade-off: easy-to-follow guidelines or more targeted guidelines that are more complex and therefore more difficult to use than previous guidelines.

This criticism is reasonable. The complexity is a result of insufficient evidence from clinical trials to make more exact and user-friendly recommendations, and also a result of the RAND/UCLA methodology. In cases that lack sufficient evidence on which to make a decision, the guideline development uses voting among experts in an attempt to develop consensus. This often results in complexity, lack of consensus, or inconsistencies.

The guidelines are straightforward for postmenopausal women and men age 50 and older on at least 7.5 mg prednisone for more than 3 months.

Since there is substantial evidence that many patients on glucocorticoid therapy go untreated, the risk of fracture in this population would be substantially reduced if clinicians would adhere to the recommendations.

The 2010 recommendations do not include transplant recipients, children, or patients on inhaled corticosteroids

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