SUPPLEMENTARY APPENDIX 1: Methods

2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Methodology Overview

This guideline was developed following the American College of Rheumatology (ACR) guideline development process (www.rheumatology.org/Portals/0/Files/ACR%20Guideline%20Manual_Appendices_updated%202015.pdf). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) (1-4).

Teams Involved

A Core Leadership Team (six members) met weekly to supervise the project and was responsible for confirming the scope and clinical (Patient/Intervention/Comparator/Outcomes – PICO) questions (see Supplementary Appendix 2), coordinating with the Literature Review Team, overseeing the voting process, and drafting the manuscript. The Core Team, together with the Literature Review Team, was comprised of individuals with content and methodological expertise, and included a GRADE methodologist who advised on the process of developing and presenting the evidence and provided input on the quality assessment of evidence and summary of findings (SoF) tables (provided in Supplementary Appendix 3).

The Literature Review Team (13 members) conducted a systematic search with the assistance of an experienced medical librarian, screened papers for relevance, assessed study quality, extracted data, computed pooled estimates of outcomes, graded the quality of evidence, generated an evidence summary for each PICO, and compiled an evidence report.

The Voting Panel consisted of 13 people, including adult and pediatric rheumatologists and endocrinologists, a nephrologist, a gastroenterologist, and 2 patient representatives. The role of the

Voting Panel was to vote on the drafted recommendation statements derived from the PICO questions, keeping the evidence report, their expertise and experience, and patient values and preferences in mind.

The ACR provided training for everyone involved in the development of this guideline, which included explanations of the ACR guideline process and GRADE methodology. See Supplementary Appendix 4 for team/panel rosters.

Disclosures and Management of Conflicts of Interest

Per ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) was required to disclose all relationships (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Glucocorticoid-Induced-Osteoporosis). Disclosures were evaluated to determine if any relationships were considered potential conflicts of interest for purposes of this project. Individuals whose primary employment (> 51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project's principal investigators (PIs) and the Literature Review Team leader had no relevant conflicts of interest for the full 12 months before this project began, and a majority of guideline development team members had no relevant conflicts of interest for the duration of the project. Intellectual conflicts, such as a prior publication or scientific presentation on glucocorticoid-induced osteoporosis (GIOP), were recognized as important and were required to be disclosed, but because they were ubiquitous, intellectual conflicts were not counted as conflicted toward the allowed threshold.

Participant disclosures were shared with each project participant via email prior to the Voting Panel meeting. Updated participant disclosures are included online with this manuscript. Finally, author disclosures are also included in this paper.

Scope and Target Audience

The scope of this project included the assessment, prevention, and treatment of osteoporosis (OP) and fractures in children and adults taking glucocorticoids (prednisone dose of > 2.5 mg of prednisone for ≥ 3 months), including patients with organ transplant who are treated with GCs. Clinical situations not addressed by this guideline include treatment of people with stage 4-5 chronic kidney disease and people who use inhaled GCs.

The target audience for this guideline includes people with or at risk for GIOP and their clinicians. Derivative products may be developed in the future to facilitate implementation of this guideline to these audiences.

Establishing Key Principles and PICO Development

The Core Team reviewed and updated the 2017 American College of Rheumatology GIOP Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (5) PICO-formatted clinical questions for this guideline update (4). Fracture (hip, vertebral, non-vertebral) and bone mineral density (BMD) were ranked as critically important outcomes for treatment evaluation. BMD, however, was considered an indirect outcome of fracture. Important outcomes included adverse effects of treatments, which included overall incidence of serious and total adverse events (AEs) in all clinical scenarios. These events included atypical femoral fracture; upper gastrointestinal AEs for bisphosphonates; osteonecrosis of the jaw; rate of transplant rejections, mortality, and hypo-or hypercalcaemia in transplant recipients; and maternal and fetal risks for women of child-bearing potential.

Framework for the GIOP Guideline Development

As in the 2017 ACR GIOP guideline, the group agreed that the scope of the populations to be addressed would include adult men and postmenopausal women and special populations that have

unique risks, such as organ transplant recipients, women of childbearing potential, children, and people receiving very high-dose GCs (defined as one or more courses of high dose GCs (initial dose of ≥ 30 mg/day of prednisone or equivalent) and a cumulative dose of ≥ 5 grams (6,7). Chronic GC use was defined as ≥ 3 months in duration. Adult men and women were divided into two groups based on age (≥ 40 years, < 40 years) because tools to predict absolute fracture risk are available only for adults ≥ 40 years. After defining population risk groups, interventions and comparators were specified for each PICO question (see list of PICO questions in Supplementary Appendix 2). The Core Team agreed that while bone mineral density (BMD) data would be examined, the critical outcome for the analysis and literature search was fracture – particularly vertebral fracture. Vertebral fractures are more common than femoral fractures in GC treated patients and GIOP clinical trials are not of adequate size to assess the impact of interventions on femoral fractures. When necessary to use BMD to support a recommendation, the Voting Panel rated down the quality of evidence for indirectness. PICO questions included assessment and reassessment of fracture risks, treatment comparisons, and questions about duration and reassessment of treatment.

Systematic Synthesis of the Literature

Literature Searches

To identify relevant evidence for the PICO questions, a medical librarian, in collaboration with the Core Team, performed systematic searches of the published English language literature. Because this guideline is an update of the ACR's 2017 GIOP guideline, which was based on a systematic literature review, this guideline focused on more recently published evidence, for the most part. OVID Medline, PubMed, OVID Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) searches were performed from April 22, 2016 through January 24, 2022 for all questions other than sequential therapy. Sequential therapy had not been included in the original search but was searched for this

guideline, from January 1, 2013 through January 24, 2022 (see Supplementary Appendix 5). For some PICO questions, such as those covering combination therapy and sequential therapy, we sought indirect evidence (i.e., evidence on non-GIOP or general population with osteoporosis) going back to April 22, 2013 when the literature searches did not identify studies assessing the use of these therapies in the GIOP population.

Study Selection

DistillerSR software (https://distillercer.com/products/distillersrsystematic-review-software/) was used to aid screening the literature search results. Teams of two independent reviewers performed duplicate screening of each title and abstract with articles identified as potentially eligible passing to review of full text. Eligible articles underwent full-text screening by two independent reviewers. Selected manuscripts were matched to PICO questions. See Supplementary Appendix 6 for details related to the study selection process.

Data Extraction and Analysis

Comparative data (e.g., from RCTs) for each PICO question was extracted into RevMan software (http://tech.cochrane.org/revman). Risk of bias of each primary study was assessed using the Cochrane risk of bias tool (http://handbook.cochrane.org/). The following outcomes were chosen as critical/important: fracture; bone mineral density (BMD, considered an indirect outcome), and treatment-related adverse events (AEs), with atypical femoral fracture; upper gastrointestinal AEs for bisphosphonates; osteonecrosis of the jaw; transplant rejections, mortality, and hypo-or hypercalcaemia in transplant recipients; and maternal and fetal risks for women of child-bearing potential considered the most important adverse events to capture.

The treatment effects from dichotomous outcomes (rate of fracture or adverse event) were calculated as relative and absolute effects with 95% confidence intervals. Relative effects capture the

difference between intervention and control in relative terms. For example, a 10% event rate in controls and a 5% event rate in the intervention represents a 50% relative risk reduction (10% - 5%/ 10%). The same difference represents a 5% absolute risk reduction (10% - 5% = 5%). For continuous outcomes (bone mineral density scores), we calculated the mean difference between groups with 95% confidence intervals.

In order to project absolute risk reduction within each risk strata, we constructed a risk calculator to display the absolute risk reduction in vertebral fracture rates over five years, depending on hypothetical baseline fracture risk ranging from 1% to 20%. We used the following cut-points to stratify levels of risk: low risk, viewed as < 5% incidence of vertebral fractures over 5 years; medium risk, 5 to < 10%; and high risk, ≥ 10%. The Voting Panel then made recommendations based on absolute fracture reduction with treatment in each of these strata. We focused on vertebral fracture rates because this outcome was more consistently reported in the literature and because of the greater effects of GCs on trabecular bone.

Evidence Report Formulation

RevMan files were exported into GRADEpro software to formulate a GRADE Summary of Findings (SoF) table for each PICO question (4), when possible. The quality of evidence for each outcome was evaluated by one literature review team member, then verified by the literature review leader (SU) using GRADE quality assessment criteria (1) with discordance resolved by discussion. The GRADE system rates the overall quality of the evidence as high, moderate, low, and very low. These ratings are based on the following GRADE domains: overall risk of bias rating of all the studies included in the evidence base, consistency of findings across studies, directness of evidence (to the population, intervention, or outcomes), and precision of the estimated effect size (typically judged by the confidence intervals surrounding the effect estimate). In situations where we used indirect evidence from a non-GIOP population (general osteoporosis) or from surrogate outcomes (bone mineral density), we rated down

the quality of the evidence for indirectness. The resulting SoF tables were compiled in an evidence report (Supplementary Appendix 3). The Core Leadership Team reviewed the evidence report and addressed possible evidence gaps prior to presentation to the Voting Panel.

Moving from Evidence to Recommendations

GRADE methodology specifies that panels make recommendations based on a consideration of the balance of benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the trade-off between desirable and undesirable outcomes; recommendations require estimating the relative value patients place on the outcomes.

A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making.

Judgments are based on the experience of the clinician panel members in shared decision making with their patients, on the experience and perspectives of the 2022 guideline Patient Panel members and, to a considerable extent, on the results of discussion with the patient group.

Consensus Building

The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. Individual online voting took place first, to ascertain initial consensus, followed by a 2-day virtual webinar meeting of the Voting Panel, where they reviewed the evidence

and provided votes on the direction and strength of each drafted recommendation. The webinar voting process was conducted using Poll Everywhere software (www.polleverywhere.com). A 70% consensus was used as the threshold for a recommendation; if 70% consensus was not achieved during an initial vote, the panel members held additional discussions before re-voting until at least 70% consensus was achieved.

Consistent with GRADE guidance, in some instances, the Voting Panel chose to provide a strong recommendation despite a low or very low-quality rating of evidence (3). In such cases, a written explanation is provided describing the reasons behind this decision with reference to GRADE guidance on the matter (3).

Final Review and Approval of the Manuscript by the ACR

In addition to journal peer reviews, the manuscript was reviewed by the ACR Guideline Subcommittee, ACR Quality of Care Committee, and the ACR Board of Directors. These ACR oversight groups did not make or mandate that specific recommendations be made within the guideline, but rather, served as peer reviewers.

Moving from Recommendations to Practice

These recommendations are designed to support health care providers who work with patients in selecting therapies. Health care providers and patients must take into consideration not only clinical phenotype and level of disease activity, but also comorbidities, response and tolerance of prior therapies, patient's values and preferences, and patient's functional status and functional goals in choosing the optimal therapy for an individual patient at the given point in treatment.

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