

DVO-Guideline

Glucocorticoid-induced Osteoporosis

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1. Introduction

1.1 Development of the guideline

In December 1999 the *Dachverband Osteologie der deutschsprachigen wissenschaftlichen Fachgesellschaften* (DVO) initiated the compilation of an evidence-based consensus guideline on the treatment of osteoporosis. Apart from the here presented version for glucocorticoid-induced osteoporosis the guideline as a whole comprises one guideline for the treatment of postmenopausal osteoporosis and one guideline for the treatment of osteoporosis in the older person (also see the introduction to the DVO-guidelines)

1.2 Objects of the guideline

are epidemiology, prevention, diagnosis, and therapy of glucocorticoid-induced osteoporosis (GIO) for patients who are treated systemically with steroids suffering from rheumatoid arthritis (RA), chronic inflammatory bowel disease, and chronic obstructive pulmonary disease (COPD). Although the recommended interventions given in this guideline are mainly guided by the duration and quantity of steroids taken, these recommendations cannot safely be applied to patients with other base diseases. The data we refer to was on the whole gained from examinations of the disease groups mentioned above and an uncritical application of these results is not advisable.

1.3 The addressees of the guidelines

are the specialists treating the base diseases, i.e. rheumatologists, pneumologists, gastroenterologists, and orthopaedists. The guideline supports the idea to refer patients who have to take steroids and who suffer from the base diseases mentioned before to specialists for counselling or for supportive treatment. The general practitioner is still responsible for the permanent care as well as for the supervision and coordination of the whole treatment. It is planned to compile a special version for general practitioners.

1.4 The aim of the guideline

is a systematic and efficient proceeding during diagnosis, prevention, and therapy of glucocorticoid-induced osteoporosis for patients (age 18 and older) suffering from rheumatoid arthritis (RA), chronic

inflammatory bowel disease, and chronic obstructive pulmonary disease (COPD), who were, are or should be treated with steroids due to their base disease.

1.5 Problems in medical care

Clinical reports indicate a considerable variation in risk evaluation, diagnosis, prevention, and therapy of steroid-induced osteoporosis and its fractures. In Germany, so far there does not exist an evidence-based consensus guideline of the 3rd development stage according to *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* (AWMF – Association of the Scientific Medical Societies in Germany) and *Ärztliches Zentrum für Qualität in der Medizin* (ÄZQ – Agency for Quality in Medicine).

1.6 Period of validity and revision of the guideline

As there is such a high dynamic in the area of research of glucocorticoid osteoporosis it seems to be appropriate to work on a first revision of this guideline 18 months after publication.

1.7 Evaluation of the guideline

Suitability for practice routine and the effect of the guideline with regard to guideline compliance (process quality) and clinical results (quality of results) as well as economic effects of the guideline – if possible - should be evaluated.

2. Methods

This guideline was compiled according to methodical requests of the ÄZQ, the AWMF, and the Scottish Intercollegiate Guidelines Network (SIGN) based on the criteria of evidence-based medicine. It is based on a systematic search and evaluation of medical literature on glucocorticoid-induced osteoporosis lead by key questions.

The **systematic literature search** was limited to HTA-reports, reviews, meta-analyses, and guidelines, which were published or revised after 1995 and before 30 June 2001. The reviews were completed by original articles, which by then had not been taken into consideration or by new ones. English and German sources were limited on “humans” and Caucasian population. In the case of epidemiological and other specific question lists, the research could be extended retrospectively till 1990 if the search did not bring up sufficient results. Search was done using search words, which were determined in line with the developed key questions.

The following **databases** were used for the systematic literature research:

- Health Technology Assessment–Databases: www.istahc.org (International Society Of Technology Assessment In Health Care (ISTHAC)); www.inahta.org (International Network of Agencies for Health Technology Assessment (INAHTA), www.dimdi.de)

- Databases for guidelines: access via www.leitlinien.de (Homepage of the ÄZQ) and the national and international links named there
- Cochrane Collaboration (also HTA database)
- Medline

The identified literature sources were selected by the abstracts and evaluated according to the "Grading System for Recommendations in Evidence-Based Clinical Guidelines" (SIGN) (see also introduction to the DVO-guidelines). If high quality meta-analyses, reviews and RCTs existed the highest level of recommendation (**A**) was given. If observational trials were used to answer the key questions (e.g. epidemiological questions) (**B**) was the highest level of recommendation which could be assigned according to the SIGN methodology. The level of recommendation (**C**) was given if less good observational trials existed the results of which were, nevertheless, in total consistent and directly applicable to the target population. Just derived evidence or evidence based on the opinion of experts can only receive level of recommendation (**D**). In addition, the SIGN definition includes so-called **good practice points**, an evaluation for recommendations for which the evidence according to SIGN-criteria is not sufficient but which are "well accepted practice" according to the conviction of the members of the guideline group. For questions for which the data showed no or extremely deviating results, the level of recommendation was additionally given with regard to a measurable increase in bone mineral density or a decrease in bone mineral density reductions.

A detailed description of the methodology for the evaluation of evidence is given in a supplement to the methodical part of this guideline.

Agreement was initially sought in the working group. All members of the working group were requested to evaluate the first draft of the guideline and to make alterations. **The consent found in this stage** was afterwards passed on to the corresponding societies of specialists and the professional associations for their comment and at the same time made public for general agreement: from July till middle of October 2002 comments on the **drafts** of the guideline could be sent to the homepage (www.bergmannsheil.de/leitlinien-dvo). All received proposals were discussed in all working groups and included in the guideline if possible.

3. Epidemiology

Osteoporosis is described as a systemic skeletal disease with a reduction in bone mass and a deterioration of the micro-architecture and a correspondingly reduced strength and increased fracture risk of the bone tissue. The WHO, however, defines osteoporosis solely by a reduction in bone mass taken from dual-energy x-ray absorptiometry (DXA) images. The threshold value for osteoporosis is a standard deviation of 2.5 and more below the average value of a reference population of young women (so-called T score). A manifest osteoporosis is characterized by an additional fracture after low trauma. We talk about osteopenia if the measured values are below -1 and above -2.5 standard deviations.

Postmenopausal osteoporosis and osteoporosis in high age are known as primary forms of osteoporosis. Secondary forms of osteoporosis are results of non-physiological influences. Among these glucocorticoid osteoporosis is the most common one. Glucocorticoids are prescribed in the case of many inflammatory systemic diseases. This guideline concentrates on three *examples* of fields of indication:

- Rheumatoid arthritis (RA),
- Chronic inflammatory bowel disease (IBD - ulcerative colitis and Crohn's disease) and
- Chronic obstructive pulmonary disease (COPD).

The frequency of these diseases and the necessity to take steroids differ:

Rheumatoid arthritis

In Northern Europe there are annual rates of incidence for rheumatoid arthritis of between 14-70 per 100,000 inhabitants. The rates of prevalence for RA in Caucasian population range between 0.3 to 1 % in the adult population. In all age groups women make up two thirds of the RA patients. More than 80 % of all RA patients are age 50 and older.

40 % of all RA patients suffer from osteopenia, approximately 20 % from osteoporosis and thus have a slightly increased risk of osteoporosis compared to people without disease. The relative fracture risk of male RA patients with high limitations in movement is stated with 1.3 and for female RA patients with 1.2.

15–20 % of all RA patients are treated with steroids at a dose of more than 7.5 mg/d. Depending on dose and duration of the steroid therapy and fracture site all RA patients show relative fracture risks between 1.2 and 5.2.

Chronic inflammatory bowel diseases

Incidence for ulcerative colitis is about 4-6/100,000 inhabitants/year, prevalence about 40-60/100,000 inhabitants in Germany. Men are slightly less affected (factor 1.01–1.4). In the majority of cases the disease starts between age 25 and 54.

In Germany, incidence for Crohn's disease is about 5/100,000 inhabitants/year. The prevalence numbers in Northern Europe differ considerably between 35-145/100,000 inhabitants. Women are 1.5–2 times more often affected than men. Falling ill is highest between age 15 and 29.

Crohn's disease and ulcerative colitis are risk factors for osteoporosis (Crohn's disease: 37 % osteoporosis; 55 % osteopenia, ulcerative colitis: 18 % osteoporosis, 67 % osteopenia).

Up to three quarters of all ill persons are treated with steroids once or several times during their illness.

Latest trials show an increased fracture risk for patients with chronic inflammatory bowel diseases (Crohn's disease and patients with ulcerative colitis), which is between 1.3 (ribs) and 1.7 (spine) depending on the fracture site. For patients with Crohn's disease the relative fracture risk is specified at 2.5. It has not yet been sufficiently examined how big the influence of a steroid therapy is.

Chronic obstructive pulmonary disease

COPD (chronic pulmonary disease) includes chronic obstructive bronchitis, pulmonary emphysema and their combinations, excludes, however, asthma bronchiale. 4–6 % of all Caucasian men and 1–3 % of all Caucasian women are affected. For Denmark the prevalence is 3.7 %, for Norway 4.5 %, and for Spain 9.1 %. For Germany a prevalence of approximately 5 % is assumed. The prevalence of non-obstructive bronchitis is estimated to be 10–15 %. Whereas the percentage of the obstructive form of chronic bronchitis compared to the overall prevalence is not exactly known.

COPD patients are increasingly less often treated with steroids. Nevertheless, there is still a number of at least 10–15 % of all patients who react to inhaled or oral steroids and need them regularly. In addition to that there is a higher number of asthma patients who need to take steroids on a regular basis due to a chronic obstruction of the respiratory tract.

72 % of all male COPD patients suffered from osteopenia and 36 % from osteoporosis. The existing data on fracture frequency of COPD patients is not satisfactory. One trial showed that in a group without steroid treatment 49 % of all subjects morphologically had at least one vertebral fracture. The percentage for subjects taking inhaled steroids was 57 % and for those taking systemic steroids 63 %. No safe data exist with regard to the degree and the frequency of steroid therapy for German COPD patients.

4. Recommendations for medical care

For all three base diseases the steroid-induced loss of bone mineral density is highest during the first six months of the therapy. In addition to that: the higher the glucocorticoid dose and the longer the therapy, the higher is the fracture risk. Nevertheless, clinical practice and latest trials let assume that – depending on the patient - the sensibility of the bone to steroids varies considerably. For patients with very high daily and cumulative steroid doses very often no measurable effects on bone and just a low fracture frequency is seen, whereas other patients suffer from fractures already at a very early stage of the initial period of low-dose steroid therapy.

>From clinical experience and based on clinical trials it seems likely to distinguish two patient groups (B):

"Incident patients" with RA, COPD or CED who for the first time or after a break of at least one year receive a steroid therapy of at least 7.5 mg/d equivalent to prednisolone for at least 6 months and those with new osteoporotic fractures which are clinically determined.

and

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"Prevalent patients" with one of the diseases mentioned above who are treated with a minimum dose of 7.5 mg/d steroids equivalent to prednisolone for at least 6 months. This group also includes patients who terminated a steroid therapy at the dosage given above less than 12 months before and who are about to restart a therapy or who are at the beginning of a new therapy.

Further prospective trials are necessary to show whether in future also patients with low steroid intake or when taking or before taking inhaled steroids have to be included into the target group of this guideline. Particularly with regard to the benefits of a therapy with bisphosphonates sufficient evidence is missing for patients at a low steroid dose.

For the assessment of the individual fracture risk further risk factors should be included and assessed by family history and physical examination (also see guideline on postmenopausal osteoporosis) apart from the base disease (duration of disease and activity as well as level of disease).

High risk factors are (B):

- Prevalent fractures and low energy trauma
- Reduction of body height > 4 cm since early adult age or > 2 cm since last measurement
- Very low weight (BMI < 20) or loss of weight of > 10 % since early adult age or since last measurement
- High fall risk
- Age > 70
- Highly limited mobility

Further moderate risk factors are (B):

- Being female
- Shortened reproductive stage of the woman, independent of the cause

So far, no risk score could be developed based on number and rating of risk factors with the help of which a proven risk assessment of osteoporosis – case-finding – with a significant prognostic value could be done. A multi-variable score based on a systematic review of risk factors for fractures, which was recently proposed by a Spanish working group still has to be evaluated with regard to application and efficiency.

In addition to family history and physical examination a base lab with the following parameters should be done:

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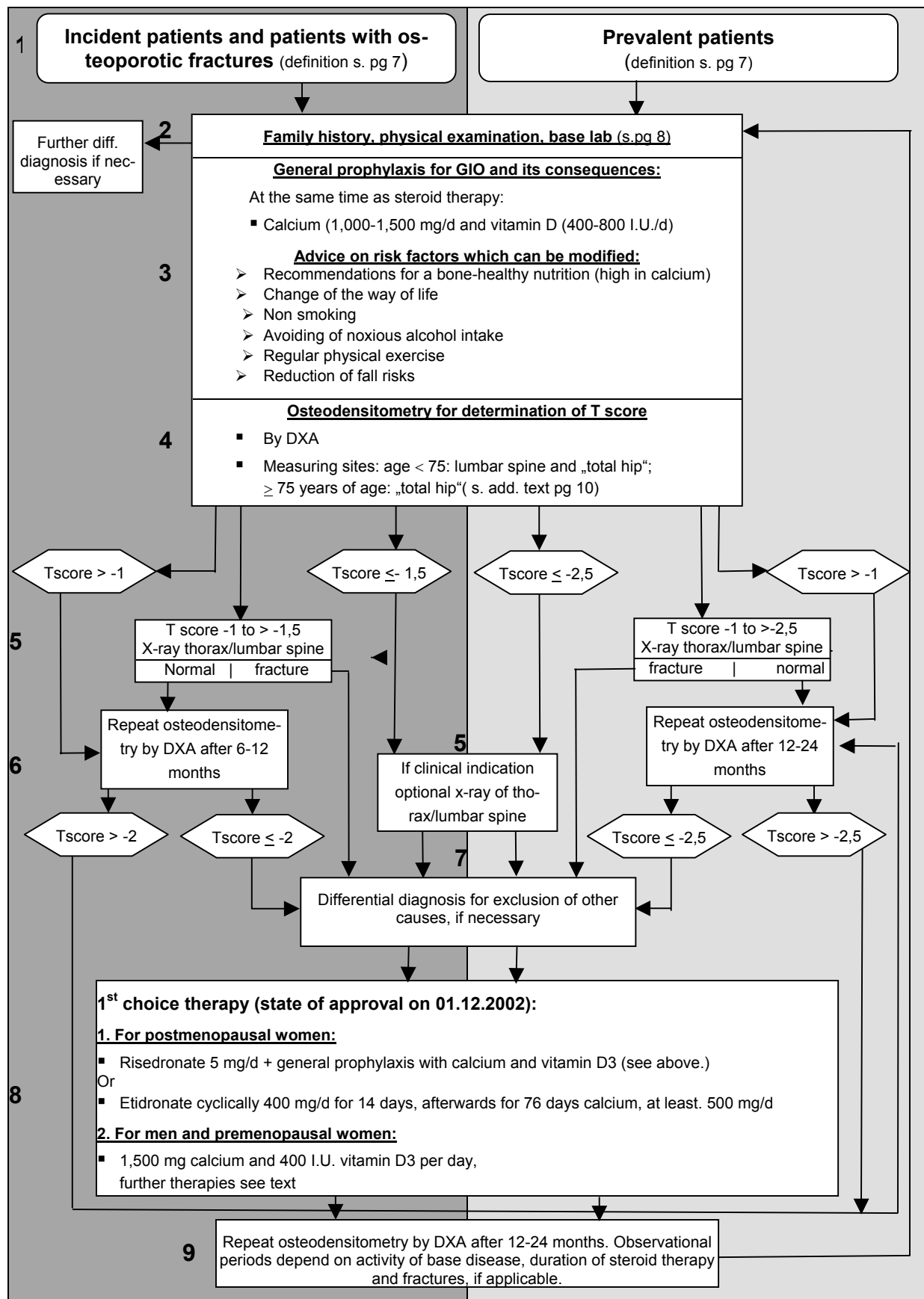
- ESR/c-reactive protein, blood count and in
- Serum: Ca, P, creatinine, AP, γ GT, basal TSH, protein immunoelectrophoresis

Cave: the TSH-value can be reduced when taking glucocorticoids.

Biomarker

At present a number of biochemical markers of the bone turnover has been examined. Their (patho)physiological interpretation, however, as well as their test features do not allow a routine application in the diagnosis of osteoporosis at present. They should only be used by specialists for differential diagnosis in special situations.

Figure 1: Clinical algorithm glucocorticoid-induced osteoporosis (GIO)



5. Comments on the algorithm

5.1 General prophylaxis for glucocorticoid-induced osteoporosis (GIO)

For patients with one of the mentioned base diseases and an “incident” or “prevalent” steroid therapy in the mentioned dose and duration it is recommended to take

- Vitamin D (400-800 I.U./d) and calcium (1,000–1,500 mg/d)
(level of recommendation **(A)** with regard to effect on bone density;
level of recommendation **(C)** for fracture reduction)

5.2 Advice to be given for risk factors that can be modified

The patient’s attention should be drawn to:

- Avoiding of alimentary lack of calcium and vitamin D
(Level of recommendation **(A)** with regard to effect on bone density;
level of recommendation **(C)** for fracture reduction)
- The risks of
underweight (BMI < 20) (**B**)
and
drastic reduction in weight (**B**),
- Measures for prevention of falls (**B**)

as well as

- The benefits of physical activity in particular with regard to reduction of fall risk (on the basis of the results of the guidelines on osteoporosis in the older person; **good practice point**),
 - Non-smoking (**B**)
- and
- Avoidance of noxious alcohol intake (**C**)

Wherever possible glucocorticoids should be

- Avoided and replaced by a sufficient, maybe intensified treatment of the base disease (**good practice point**).

5.3 Measurement of bone mineral density

For all incident and prevalent patients the indication for a measurement of bone mineral density is a direct result when taking steroids (**B**). Due to the osteoporosis definition of the WHO and the methods used in most diagnostic and therapy trials a DXA measurement is recommended. Persons below age 75 should be measured at the lumbar spine and the total hip, persons at age 75 or older should in the first place only be measured at the total hip (**D**). If this measurement results in a T score of –2.5 or below no measurement at the spine is necessary (**D**). If the T scores are between –1 and above –2.5 for prevalent pa-

tients and between -1 and above -1.5 for incident patients a measurement of the lumbar spine should be done, however, in order to avoid the risk to overlook fractures at the lumbar spine. The instructions for standardization and quality assurance of DXA measurements are strictly to be followed or in cases where they are incomplete have to be further developed (e.g. population-related and gender-specific reference groups, determination of institution-specific precision values and consideration of these when determining intervals for follow-up visits). Results are to be given in T score, i.e. related to young healthy adult reference persons.

If patients do not want to take therapeutic consequences based on the measuring result after they had been informed about the duration, methods and risks of possible therapies they do not need to be measured.

DXA is the method of choice. Based on present data QCT and osteosonometry can neither be recommended for primary diagnosis nor for therapy control.

5.4 X-ray

An x-ray of the thorax and the lumbar spine is indicated for the discovery of vertebral deformities typical of osteoporosis for incident patients with T scores between -1 and > -1.5 and for prevalent patients with T scores between -1 and > -2.5 (**D**). If the bone density values are in the area where treatment is necessary (≤ -1.5 for incident and ≤ -2.5 for prevalent patients) an x-ray of the vertebral and lumbar spine should be done if the reduction in height is above 4 cm or in the case of skeletal deformities typical of fractures (**D**).

5.5 Differential diagnosis for the exclusion of other secondary forms of osteoporosis

If bone density is reduced other diseases associated with osteopenia/osteoporosis and / or steroid therapy, such as osteomalacia, myeloma, renal osteopathy have to be excluded.

5.6 Indications for medical prevention and therapy

5.6.1 Indications for „incident“ cases and those with osteoporotic fractures

If the DXA measurement results in a T score of ≤ -1.5 for incident patients (**D**), the guideline recommends to start a medical treatment aimed at prevention in order to reduce fractures. The intervention threshold is lower for incident patients as they have a much higher reduction of bone mineral density during the first months after steroid therapy (**B**). The intervention threshold also applies to prevalent patients if they already have an osteoporotic fracture as there is a far higher risk for further fractures due to the prevalent fracture (**B**). (For incident patients with fractures no deviating procedure is necessary (**D**).)

5.6.2 Indications for prevalent cases

For this group of affected persons the guideline recommends an intervention threshold at a T score of ≤ -2.5 (**D**). In this case bisphosphonates are the first therapeutic agent to be chosen (see above). If the measuring results are more favourable apart from general prevention measures it is advised to wait.

5.7 Recommendations for therapy

- At present (middle of 2002) first choice therapeutic agents for postmenopausal women are the bisphosphonates risedronate and etidronate.
(Level of recommendation **(A)** with regard to bone density;
level of recommendation **(D)** with regard to fracture reduction.)
- In Germany approval was given for risedronate and etidronate for the treatment of glucocorticoid osteoporosis only for postmenopausal women. Trials for the efficiency of alendronate in the case of steroid-induced osteoporosis exist (see Fig. 2), approval, however, is restricted to the treatment of postmenopausal osteoporosis and osteoporosis in men.
- Dosages:
Risedronate: 5 mg/d + general prevention by calcium and vitamin D3 (s. algorithm)
Etidronate: cyclically 400 mg/d for 14 days afterwards for 76 days at least 500 mg Ca.
- At present it should be calculated with a treatment duration of two to three years. For longer or shorter therapies sufficient data does not exist.

For men and premenopausal women with glucocorticoid-induced osteoporosis no approval was given for bisphosphonates so far. Alendronate was approved for the treatment of osteoporosis in men without further distinction of the genesis of the osteoporosis. The approval situation is not consistent in this case as there are separate approvals for glucocorticoid-induced osteoporosis for postmenopausal women. For the groups mentioned above we refer to existing trials (see following table and tables 3-6 in the annex). When prescribing bisphosphonates for the groups mentioned above the procedures of a so-called “off-label” usage have to be taken into consideration.

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Table 1: Situation of approval and trials for the therapies recommended

Drug	Dosage	Approval	No Approval for	Level of Recommendation based on Trial Situation
Etidronate	400 mg/cycl. + 500 mg calcium	- Treatment of postmenopausal osteoporosis - For postmenopausal women treatment of glucocorticoid-induced osteoporosis	- Men - Premenopausal women	With regard to bone density - Men: (A) - Premenopausal women: (A) - Postmenopausal women: (A) With regard to fracture reduction - Men: (D) - Premenopausal women: (D) - Postmenopausal women: (D)
Risedronate	5 mg/d + general prevention	- Treatment of postmenopausal osteoporosis - For postmenopausal women treatment of glucocorticoid-induced osteoporosis	- Men - Premenopausal women	With regard to bone density - Men: (A) - Premenopausal women: not sufficient evidence - Postmenopausal women: (A) With regard to fracture reduction - Men: (D) - Premenopausal women: not sufficient evidence - Postmenopausal women: (D)
Alendronate	10 mg/d + general prevention	- Treatment of postmenopausal osteoporosis - Treatment of osteoporosis in men	- Treatment of glucocorticoid-induced osteoporosis - Premenopausal women	With regard to bone density - Men: (A) - Premenopausal women: (A) - Postmenopausal women: (A) With regard to fracture reduction a) vertebral fractures - Men: (D) - Premenopausal women: (D) - Postmenopausal women: (D) b) peripheral fractures - No significant reduction for any group

Details on the trials from which this information was taken can be found in tables 3-6 in the Annex.

5.8 Alternative therapies

If bisphosphonates taken daily are not tolerable it is often changed to weekly oral or intravenous intake. In these cases the modalities of the “off-label-use” have to be followed.

Table 2: Situation on approval and trials for weekly and intravenous intake

Drug	Dosage	Approval	No Approval for	Level of Recommendation based on Trial Situation
Risedronate	35 mg/week orally	Treatment of postmenopausal osteoporosis	- Treatment of glucocorticoid-induced osteoporosis a) of men b) of postmenopausal women c) of pre-menopausal women	The efficiency of a weekly intake of 35 mg risedronate has not been examined for steroid subjects. According to the opinion of experts the trial results of daily intake of risedronate (for steroid subjects) can be applied to the weekly intake (level of recommendation see table 1) due to the bio-equivalence.
Alendronate	70 mg/week orally	Treatment of postmenopausal women	- Treatment of the glucocorticoid-induced osteoporosis a) of men b) of postmenopausal women c) of pre-menopausal women	The efficiency of a weekly intake of 35 mg alendronate has not been examined for steroid subjects. According to the opinion of experts the trial results of daily intake of alendronate (for steroid subjects) can be applied to the weekly intake (level of recommendation see table 1) due to the bio-equivalence
Pamidronat	90 mg i.v.	tumour-induced hypercalcaemia, osteolytic bone metastases, multiple myeloma stage III, Paget's disease of the bone	Treatment of osteoporosis	Trial population too small. Evidence-based recommendations not possible (also see table 6 in the Annex)

Further medical alternative therapies are calcitonin, alphacalcidol/calcitriol and fluorides. No recommendation can be given for a postmenopausal hormone therapy for the prevention of osteoporosis especially with combination medicine due to the side effects observed in the Women's Health Initiative trial. Further information on this and other alternative drugs **can be found in an additional documentation of this guideline** and in the guideline on postmenopausal osteoporosis.

The quick improvements to be expected in the prevention and therapy of steroid-induced osteoporosis have to be taken into consideration.

5.9 Non-medical therapy alternatives

Only data from experts exist for movement therapy, physiotherapy, and physical therapy. These confirm the clinical benefit of these measures (*good practice point*).

5.10 Therapy control

5.10.1 Incident patients

It is recommended to check the result of the therapy after 12 to 24 months by DXA and to adjust it if there is still a loss of bone density (periods for follow-up measurements depend on the course of the disease and the steroid therapy of the individual patient). For measurement results above the intervention threshold it is recommended to attentively watch the situation and to repeat the measurement already after 6 to 12 months (**D**). Is the result at -2 SD or below it is generally indicated to follow the medical prevention described above (**D**). If the results are above the intervention threshold and the steroid therapy is continued the recommendations for the management of “prevalent” cases should be followed (**D**).

5.10.2 Prevalent patients

A follow-up measurement should just be done 12 to 24 months after the initial measurement (**D**). If individual courses without measurable influence of the steroids on bone density of a patient are seen (resistant to steroids) even bigger intervals for follow-up measurements are possible based on the risk assessment for the individual subject (**D**).

5.11 Termination of preventive treatment and control examinations

A treatment with bisphosphonates for a period of more than three years needs an extraordinary indication. Efficiency and risks of a long-term therapy are not sufficiently examined at present. Indications for therapy are based on the results taken from later examinations of the patients.

If the steroid therapy is terminated for „incident“ and „prevalent“ cases a high risk factor is ruled out. Depending on the results of control bone density measurements, the initial bone density and the existence of further high risk factors it is to be decided whether to continue the bisphosphonate therapy.

Is the steroid therapy re-started within 12 months the patient is to be considered as a “prevalent” case. If it is re-started at a later date, again as “incident”.

5.12 Undesired effects of drugs and interactions:

Contraindications and rules for intake (here especially with bisphosphonates) of the recommended drugs have always to be kept to.

In general, long-term effects of bisphosphonates have not yet been sufficiently examined. Women of childbearing age should only be treated with bisphosphonates in the case of reliable contraception.

6. Open questions and need for research

The data on fracture reduction by bisphosphonates is still insufficient. Alendronate showed comparable results as etidronate with regard to efficiency on bone density but is not approved for the treatment indication "glucocorticoid-induced osteoporosis". Insecurities with regard to a treatment with bisphosphonates over a longer period of time have been pointed out.

For further agents such as calcitonin, alfacalcidol, fluorides, hormone replacement therapy, and parathyroid hormone the existing data for the assessment of the efficiency of treatment of glucocorticoid-induced osteoporosis is insufficient. This also applies to the same extent to combinations of the given agents with each other or especially with bisphosphonates.

For SERMs, anabolic steroids, and inhibiting hormones no data was found regarding the importance of these agents for the treatment of RA, IBD, and COPD patients with steroid-induced osteoporosis.

The existing data on fracture incidence (and falls) for patients with one of the three base diseases taking into consideration prior or prevalent fractures, different initial values of bone density, and different steroid intake (daily, cumulative) is especially unsatisfactory. Trials on the frequency of steroid sensibility and for the identification of patients sensible to steroid could help in future to determine the different risks of osteoporosis of glucocorticoid patients and to give reliable intervention thresholds for therapy.

So far trials are missing which allow an unequivocal determination of T scores for prevention and therapy thresholds.

Furthermore, the question has not been answered how patients with osteoporotic fractures with normal or slightly reduced bone density should be treated. Are bisphosphonates indicated for treatment?

In view of the high number of persons concerned further trials in the research field named above are to be undertaken.

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Table 3

Etidronate										
Level of recommendation (A) for postmenopausal women (preventive and therapeutic approach) at "bone density outcome"; for men and premenopausal women level of recommendation (A) (preventive approach only) at "bone density outcome"; level of recommendation (D) at "outcome fracture reduction" for men, postmenopausal and premenopausal women										
Trial	Type of Trial	Dosage	Total Trial Population n	Post-menop n	Pre-menop n	Men n	Results BMD	Evidence BMD (SIGN)	Results Fractures	Evidence Fractures (SIGN)
Adachi et al. J.Rheum. 2000	Pooled Data Analysis from 3 prevention trials (PT) and 2 therapy trials (TT)	cyclically intermittent 400mg/d f.16 d then 97-500 mg Ca++ f. 76 d (Ca dosage depending on alimentary Ca intake)	PT* with n=286; Etidr n=141 Plac n=145 out of these RA subjects. n=89 Etidr.n=43 Plac.n=46 gastroint. subj. n=8 Etidr.n=2 Plac n=6 TT * with n=86 Etidr. n=44 Plac n=42 out of these RA subjects. n=12 Etidr.n=3 Plac.n=9	PT n=144; Eti. n=72 Plac.n=72 TT n=71 Eti. n=40 Plac. n=31	PT n=35; Eti. n=18 Plac. n=17 TT n=6 Eti. n=4 Plac. n=2	PT n=107 Eti. n=51 Plac. n=56 TT n=19 Eti. n=10 Plac. n= 9	"first outcome"; for subjects with etidronate the prevention trials showed no considerable changes in bone density, whereas subjects taking placebo showed loss in bone density after 52 weeks. The average difference in bone density after therapy compared with the placebo group at lumbar spine is 3.7% +/- 0.6%(p< 0.001), at femoral neck 1.7% +/- 0.7% p=0.012 and at trochanter 2.8% +/- 0.7% (p<0.001); Sub-group analyses for men and premenopausal women showed significantly positive therapy effects. The therapy trials showed a significant increase in bone density at the lumbar spine after 52 weeks of 4.8% +/- 1.0% (p<0.001) and of 5.4% +/- 1.5 % (p<0.001) after 104 weeks., for postmenopausal women of 6.3% +/- 1.7% (p<0.001). For men no differences from the initial measurements were seen. Due to the small number of cases no evaluation could be done for premenopausal women. Evaluation RA subjects. (N=76): Increase in bone density: 3.9% +/- 1.0%, p< 0.001. Evaluation gastrointest. subjects. (N=8): Increase in bone density: 3.2% +/- 12%; p<0.032.	For postmenopausal women in preventive as well as in therapeutic approach 1++; for men only in preventive approach 1++; in therapeutic approach 1-; for premenopausal women also only in preventive approach 1+ (very small trial population), in therapeutic approach 1-.	"second outcome"; preventive approach: no significant results for the reduction of vertebral fractures in the total population and in the group of men. In the group of postmenopausal women the RR for vertebral fractures after etidronate therapy was 0.19 (95% CI 0.04-0.81; with 2 of 63 compared to 11 of 65 subjects). There were no vertebral fractures in the group of premenopausal women. The reduction of peripheral fractures did not reach significance in any of the groups (0.77 (95% CI 0.25-2.35). The overall number of fractures of the subjects of the therapy trial was too low for a valid statistical analysis.	Fracture was just second outcome, results only from pooled data. A second analysis of the main trials did not result in significance for fracture reduction. Whether this second analysis or the original calculation is the basis for the results of the meta-analysis cannot be seen from the information given in the trial. 1-

*PT = Prevention Trial *TT = Therapy Trial

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Table 4a

Alendronate										
Level of recommendation (A) for subjects treated with glucocorticoid in a preventive and therapeutic approach with "bone density outcome; level of recommendation (D) at outcome "fracture reduction" due to methodical insufficiencies of the trial or missing data.										
Trial	Type of Trial	Dosage	Total trial Population	Postmenop n	Premenop n	Men n	Results BMD	Evidence BMD (SIGN)	Results Fractures	Evidence Fractures (SIGN)
Saag et al. NEJM 1998	RCT; multi-national multi-center trial, duration of trial 48 months	All subjects received 800-1,000 mg elementary calcium and 250-500 I.U. vitamin D; 34% of the women received in addition an oestrogen substitution.	n= 477; alendr. 5 mg n=161; alendr. 10 mg n=157; placebo n=159; in addition in the multi-national part of the trial a trial population was treated with 2,5 mg alendronate, for whom only a low, non-significant increase in bone mineral density could be seen. Number of RA subjects at the total trial population approx. 30%; IBD subj. = approx. 5%; COPD subj. = approx. 3% (asthma subj. = approx. 8%)	Alendr. 5 mg n=82; alendr. 10 mg n=83; placebo n=67	Alendr. 5 mg n=34; alendr. 10 mg n=30; placebo n=40	Alendr. 5 mg n=45; alendr. 10 mg n=44; placebo n=52	"first outcome"= measurement of bone density by DXA at the lumbar spine; further BMD measuring sites = femur, trochanter and total body; after 48 months a significant increase in bone density could be seen in the groups taking 5 mg and 10 mg at the lumbar spine (5 mg-group +2.1±0.3%; p≤0.001/ 10 mg-group +2.9±0.3%; p≤0.001) at the femur (5 mg-group +1.2±0.4%; p≤0.01 and p≤0.001/ 10 mg-group +1.0±0.4%; p≤0.01 and. p≤0.001) and at the trochanter (5 mg-group +1.1±0.3%; p≤0.01 and p≤0.01/ 10 mg-group +2.7±0.4%; p≤0.001 resp. p≤0.001) compared to the initial values as well as to the placebo group. Separate analysis of the postmenopausal and premenopausal women and men showed a clear increase in bone density but no p-values were given for these sub-groups. 80% of the subjects in the alendronate group showed an increase in bone density at the lumbar spine, compared to 45 % in the placebo group.	The efficiency of alendronate on bone density at the lumbar spine was proved. Unfortunately, significance values for evaluations for gender and hormone situation are missing. 1++	Second outcome: morphometrically and semi-quantitatively recorded vertebral fractures	The incidence of morphometrically defined vertebral fractures in the alendronate group (5 mg + 10 mg) was not significantly lower than in the placebo group (RR= 0.6; CI= 0.1–0.4); there was neither a significant difference between alendronate subjects and placebo subjects with regard to frequency of the semi-quantitatively recorded vertebral fractures (p=0.18). Limited significance for vertebral fractures in the group of postmenopausal women (p=0.05), but when evaluating vertebrae semi-quantitatively the frequency of extra-vertebral fractures is the same in both groups (4.4%). 1-

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Table 4b

Alendronate	Level of recommendation (A) for subjects treated with glucocorticoids in a preventive and therapeutic approach with "bone density outcome"; level of recommendation (D) with outcome "fracture reduction" due to methodical insufficiencies of the trials or missing data									
Trial	Type of Trial	Dosage	Total Trial Population n	Postmenop n	Premenop n	Men n	Results BMD	Evidence BMD (SIGN)	Results Fractures	Evidence Fractures (SIGN)
Adachi et al. Arthritis & Rheumatism 2001	Multi-national RCT; placebo-controlled 12-months extension of a previous trial	2.5 mg, 5 mg or 10 mg alendronate/d; and for all subjects including placebo subjects 800-1,000 mg Ca++ and 250-500 I.U. vitamin D per day	initially 560 subjects. after 12 mo. 476 subjects;. in the 2 nd year initially 208 subjects; 80 % participated till the end of the trial (n=166); ALN 2.5 mg/d n=29 (remaining subjects changed to 10 mg-group); ALN 5,0 mg/d n=63; ALN 10 mg/d n=55; placebo n=61	ALN 2.5/10 mg/d n=10; ALN 5 mg/d n=29; ALN 10mg/d: n=26, placebo:n=25	ALN 2.5/10 mg/d n=5; ALN 5 mg/d n=16; ALN 10mg/d n=14; placebo n=17	ALN 5/10 mg/d n=14; ALN 5mg/d n=18; ALN 10mg/d n=15; placebo n=19	Those subjects in the ALN 10 mg -group who had only been taking steroids for less than 4 months had a significant (p< 0.05) increase in bone density of 6.8% (spine), 7.7% (femur), 9.4% (trochanter) und 2.4% (total body); The ALN 5mg-group showed lower (but not significant) differences compared to the initial measurement. Men showed an approx. 2 % higher increase in bone density at the spine than women (p<0.01), with an approximately similar treatment impact for both genders compared to the placebo group. Increases in bone density were also seen for premenopausal women (statements referring significance were not found)	The effect on bone density could be proved for women and men in the preventive as well as in the therapeutic approach. 1++	In total, there were only very few fractures during the 24 months of the trial: after 2 years in the placebo-group 4/59 (6.8%) in the ALN-groups 1/143 (0.7%)(p=0.026). Most happened in the group of postmenopausal women; 6 non-vertebral fractures happened in the placebo-group (9.8%; n=61) and 8 in the ALN-groups (5.,4%; n=147) (not significant).	A significant reduction of vertebral fractures ("second outcome") could be demonstrated. The number of fractures and of the follow – up after 24 months was, however, low: 1 vertebral fracture in the alendronate group of 5 mg and 10 mg (n=143; 0.7%) versus 4 vertebral fractures in the placebo group (n=59; 6.8%) with p=0.026; not sufficient significance for the sub-groups. No significant reduction could be proven when undergoing ALN therapy. 1-
Haderslev et al. Gastroenterology 2000	RCT	ALN 10 mg/d; 400 I.U. vitamin D and Ca++, if the daily individual Ca++-intake <1,000mg/d; placebo group was analogously given vitamin D and Ca++ for 12 months	ALN-group n=15; placebo group n=17; Crohn's disease-subjects	ALN n=3; placebo n=4	ALN n=7; placebo n=9	ALN n=5; placebo n=4	Difference in bone density at the lumbar spine of therapy groups and placebo group of 5.5% (p>0.01); 66% (p<0.001) was the difference when measuring the total spine. Increase in bone density could be seen in all groups. Increase in BMD at the hip 3.2% (p=0.08).	Overall trial population is very small. The results with regard to impact on bone density are, however, consistent with the data from Adachi (s.a.) 1+	At the beginning of the trial 12 % of the placebo group had vertebral fractures and 33 % of the alendronate group (p=0.60). In the course of the trial there were 2 vertebral fractures in the placebo group and 1 vertebral fracture in the alendronate group. No usable statements on peripheral fractures.	No statements on fracture reduction possible.

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Table 5a

Risedronate Level of recommendation (A) for men and postmenopausal women with "bone density outcome" , level of recommendation (A) for men and postmenopausal women with "bone density outcome" , level of recommendation (D) with outcome "fracture reduction" due to methodical insufficiencies or missing data										
Trial	Type of Trial	Dosage	Total Trial Population n	Postmeno n	Pre-menop n	Men n	Results BMD	Evidence BMD (SIGN)	Results Fractures	Evidence Fractures (SIGN)
Reid et al. J.Bone Miner.Res. 2000	RCT; duration of the trial 12 months, exclusively therapeutic approach with subjects who had received steroids for at least 6 months.	2.5 mg/d or 5 mg/d and in addition 400 I.U. vitamin D and 1,000 mg Ca++, this also applies to the placebo group. After 6 months the 2.5 mg-group was included in the 5 mg group.	N=290; ris 2.5 mg n=94; ris 5 mg/d n=100; placebo n=96	2.5 mg/d n=48; 5.0 mg/d n=55; placebo n=53	2.5 mg/d n=9; 5 mg/d n=9; placebo n=7	2.5 mg/d n=37; 5 mg/d n=36; Placebo n=36	"first outcome" after 12 months the mean measured bone density had not changed at the lumbar spine, femur and trochanter of the subjects of the placebo group. Taking 5 mg/d of risedronate resulted in an improvement compared to the placebo group at the lumbar spine 2.7% +/- 0.67% (p<0.05), at the femur 1.9% +/- 0.67% (p<0.01) and at the trochanter 1.6% +/- 0.81% (p<0.05). In the 2.5 mg-group the bone density differences compared to the placebo group were not significant. The efficiency could be proved for the group of men and postmenopausal women. The group of treated premenopausal women was regarded as being too small for relevant statements.	For men and postmenopausal women a significant increase in bone density could be proved for a therapy taking 5 mg/d. 1++	"second outcome" during the 12 months of the trial 9 out of 60 (15%) placebo subjects and 3 out of 60 subjects (5%) in all other dosage groups suffered a fracture. The decrease of vertebral fractures compared to placebo was 70% (p=0.125) in the 2.5 mg group as well as in the 5 mg group. Only if both dosage groups are evaluated together a significant fracture reduction could be seen p= 0.042. 6 subjects of the placebo group, 8 subjects of the 2.5 mg-group and 8 in the 5mg-group suffered non-vertebral fractures at similar skeletal sites,. With regard to fracture frequency only approximately one third of the placebo and therapy groups was evaluated without further comment.	The efficiency of risedronate with regard to a reduction of the frequency of vertebral and peripheral fractures could not be finally proved .1-
Wallach et al. Calcified Tissue Int. 2000	RCT; trial data from Reid et al.(s.a.) and in addition the preventive part (Trial of Cohen(Tab.5b)) (subjects who received steroids for less than 3 months) but apart from this equal trial design	s.a.	N=518; 2.5 mg/d n= 165; 5mg/d n=174; placebo n=170	2.5 mg/d n= 79; 5 mg/d n=88; placebo n=88	2.5 mg/d n=25; 5 mg/d n=23; Placebo n=22	2.5 mg/d n=61; 5 mg/d n=63; placebo n=60	"first outcome" compared to placebo taking 5 mg/d of risedronate lead to an improvement of 2.9% (p<0.001), at the femur 2.8% (p<0.001) and at the trochanter 2.8% (p<0.001). Bone density at the distal radius could be kept constant in the 5 mg group whereas subjects of the placebo group lost significantly bone mass. In total the 2.5 mg dosage showed a lower efficiency and resulted only at the lumbar spine in a significant increase in bone density compared to the placebo group. The positive treatment effects on bone density were significant in the therapeutic as well as in the preventive part. Statistically valid statements for premenopausal women cannot be made due to the low number of women examined in these groups.	A significant increase in bone density could be proven for men and women taking 5 mg/d of risedronate. 1++	Results also see above. In the preventive part of the trial there was a fracture reduction of 71% (3 fractures in the risedronate group compared to 9 fractures in the placebo group, p=0.07). Both therapy parts together reached significance in the 5 mg-group p=0.01. In the combined evaluation of the data from the prevention and the therapeutic part, however, also only 2 thirds or the half, respectively, of the subjects was included.	The data of both study parts were combined post hoc. A proof of fracture reduction could not finally be given due to methodical insufficiencies for risedronate.1-

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Tabelle 5b

Risedronate Level of recommendation (A) for men and postmenopausal women with bone density outcome ", level of recommendation (D) with outcome "fracture reduction" due to methodical insufficiencies of the trials or missing data										
Trial	Type of Trial	Dosage	Total Trial population n	Post-menop n	Pre-menop n	Men n	Results BMD	Evidence BMD (SIGN)	Results Fractures	Evidence Fractures (SIGN)
Cohen et al. Arthritis & Rheumatism 1999	RCT; Trial with preventive approach with subjects who have been taking steroids for less than 3 months	2.5 mg/d or 5 mg/d and in addition also for the placebo group 500 mg Ca++	N=228 ; 2.5 mg/d n=75; 5mg/d n=76; placebo n=77	2.5 mg/d n=33; 5 mg/d n=35; placebo n=37	2.5 mg/d n=17; 5mg/d n=14; placebo n= 15	2.5 mg/d n=25; 5 mg/d n=27; placebo n=25	"first outcome" In the placebo group the subjects lost approx. 3% of the initially measured bone density at the lumbar spine, the femur and the trochanter. Compared to the placebo group differences in bone density were seen in the 5mg-group at the lumbar spine of 3.8% +/- 0.8%, at the femur of 4.1% +/- 1.0% and at the trochanter of 4.6% +/- 0.8% (for all p<0,001). Changes in the 2.5 mg group were not significant. The sub-group analysis showed similarly significant results for men and postmenopausal women. The bone density of premenopausal women was significantly reduced at the lumbar spine in the placebo group, whereas the mean bone density values of the 5 mg group stayed constant after 12 months. This effect was seen at all measuring sites but, however, did not reach statistical significance.	A significant increase in bone density could be proven for men and postmenopausal women undergoing a therapy with 5 mg/d of risedronate. 1++	"second outcome" Non-vertebral fractures were reported for similar skeletal sites from 4 subjects of the placebo group, 3 of the 2.5 mg group, and 3 of the 5 mg group. Compared to the placebo group there was a non-significant fracture reduction of 71% (p=0.072) with 5.7% compared to 17.3% This tendency could also be seen in the sub-group of men and of postmenopausal women. None of the premenopausal women had a vertebral fracture.	The efficiency of risedronate with regard to the reduction of the frequency of vertebral or peripheral fractures could not finally be proven. 1-
Eastell et al. Osteoporosis Int. 2000	RCT; therapeutic approach with subjects who had been receiving steroids on a long-term basis; 2 years of therapy and 1 year follow-up without treatment	with 2.5 mg/d or 15 mg cyclically in 2 out of 12 weeks; no vitamin D and calcium	n=120; 2.5 mg n=40; 15mg n=40; Placebo n=40	n=120; subjects with Rheumatoid Arthritis	n=0	n=0	Bone density was measured every 12 weeks. After 97 weeks a significant difference in bone density could be seen in the 2.5 mg group compared to the placebo group at the lumbar spine and the trochanter. In the 15 mg group the bone density difference was only significant at the trochanter. The difference between the two therapy groups was not significant. During follow-up after termination of therapy both therapy groups and the placebo group showed losses in bone density. As a tendency it was seen that subjects of the therapy group lost more bone mass than placebo subjects. This loss of bone density only reached significance in the 15 mg group at the lumbar spine.	The increases in bone density did not reach significance at all measuring sites. 1+	No data	-

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Table 6

Pamidronat i.v. Level of recommendation: at this point in time a therapy of GIOP with intravenous Pamidronat cannot generally be recommended										
Trial	Type of Trial	Dosage	Total Trial Population n	Postmenop n	Premenop n	Men n	Results BMD	Evidence BMD (SIGN)	Results Fractures	Evidence Fractures (SIGN)
Boutsen et al., Calc Tissue Int, 1997	RCT, not blinded	Initially at the beginning of the trial and the steroid therapy 800 mg Ca++ for therapy and control group	n= 32 ; to be evaluated in the therapy group n= 14 and in the control group n=13; distribution of base diseases in therapy and control group: TG: 4 PMR, 3 AT, 3 RA , 2 CED, 2 others CG: 5 PMR, 2 AT, 3RA, 3 others	Therapy group: n=10 (out of which 3 with hormone replacement therapy at the same time) Control group: n=9 (2 of which with HRT)	TG: n=1 CG: n=2	TG: n=3 CG: n=2	"first outcome"; bone density measurement by DXA (variation coefficients between 0.75% and 0.82%) at L1-L4, femoral neck, "total hip", trochanter, intertrochanter and Ward's triangle initially with commencement of the trial and after 3, 6, 12 months. Preventive approach which included that subjects who receive steroids for the first time (10-80 mg/day) received Pamidronat i.v. at the same time Results: Significant increase in bone density after 12 months in the therapy group at the lumbar spine of 3.6% and at the femoral neck of 2.2%, compared to the control group with a significant reduction in bone density at both measuring sites by 5.3%. The infusion therapy was well-tolerated. Non of the subjects got fever or myalgia. No thrombophlebitis occurred. One subject of each group got a hypercalciuria, however, with simultaneous known alimentation poor in sodium.	The trial quality is high. The trial population, however, is very small. An evidence-based recommendation cannot be given on the basis of this trial.	X-rays of the lateral thorax and lumbar spine were done and it was looked for asymptomatic vertebral fractures (evaluation according to Minne et al.). After 12 months no new vertebral fractures could be morphologically seen in neither of the groups. One postmenopausal subject (without HRT) from the calcium group suffered, however, a non-traumatic vertebral fracture.	Evaluation of the fracture results not possible
Boutsen et al., J Bone Mineral Research 2001	RCT, not blinded	Group A: receives initially 90 mg i.v; group B receives 30 mg Pamidronat every 3 months and group C receives only 800 mg Ca++ per day, which the subjects of the other groups in addition receive as basic medication	n= 27; 9 subjects each group	n=3 per group, out of which one female subject with HRT per group	n=1 per group	n=4 per group	Trial question: Which dosage of Pamidronat i.v. has a positive effect on the development of bone density when taking steroids (base diseases: mainly diseases in the rheumatic field (2 RA subjects in the dosage group "every 3 months", 2 CED subjects in the single dosage group) Results: Significant increases in bone density were seen in both Pamidornat therapy groups after 12 months (at the lumbar spine 1.7 % in group A and 2.3% in group B, at the femoral neck 1.2% for both groups and in the "Total hip"-region 1.0% or. 2.6%, respectively; differences in the therapy groups but not significant). The group lost at the same time significantly bone density: -4.6% at the lumbar spine and -3.1% at the femoral neck.	The main aim of this trial is the comparison of the different Pamidronat therapies, single, initial taking or all 3 months for 12 months in total. No significantly different effects on bone density could be seen. An increase in bone density when taking Pamidronat compared to Ca++ is obvious but again the trial population is too small.	See trial description above; trial design identical. In the course of the trial no morphologically diagnosed vertebral fractures were seen.	Evaluation of the fracture results not possible