ARD Online First, published on March 1, 2016 as 10.1136/annrheumdis-2015-208916

Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force

Cindy Strehl,[1] Johannes W J Bijlsma,[2,3] Maarten de Wit,[4] Maarten Boers,[3,5] Nele Caeyers,[6] Maurizio Cutolo,[7] Bhaskar Dasgupta,[8] William G Dixon,[9] Rinie Geenen,[10] Tom W J Huizinga,[11] Alison Kent,[12] Annette Ladefoged de Thurah,[13] Joachim Listing,[14] Xavier Mariette,[15,16] David W Ray,[17] Hans U Scherer,[11] Raphaèle Seror,[15,16] Cornelia M Spies,[1] Simon Tarp,[18] Dieter Wiek,[19] Kevin L Winthrop,[20] Frank Buttgereit[1]

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2015-208916).

For numbered affiliations see end of article.

Correspondence to
Dr Cindy Strehl, Department of Rheumatology and Clinical Immunology, Charité University Hospital, Charitéplatz 1, Berlin 10117, Germany; cindy.strehl@charite.de

Received 18 November 2015
Revised 25 January 2016
Accepted 13 February 2016

ABSTRACT

There is convincing evidence for the known and unambiguously accepted beneficial effects of glucocorticoids at low dosages. However, the implementation of existing recommendations and guidelines on the management of glucocorticoid therapy in rheumatic diseases is lagging behind. As a first step to improve implementation, we aimed at defining conditions under which long-term glucocorticoid therapy may have an acceptably low level of harm. A multidisciplinary European League Against Rheumatism task force group of experts including patients with rheumatic diseases was assembled. After a systematic literature search, breakout groups critically reviewed the evidence on the four most worrisome adverse effects of glucocorticoid therapy (osteoporosis, hyperglycaemia/diabetes mellitus, cardiovascular diseases and infections) and presented their results to the other group members following a structured questionnaire for final discussion and consensus finding. Robust evidence on the risk of harm of long-term glucocorticoid therapy was often lacking since relevant study results were often either missing, contradictory or carried a high risk of bias. The group agreed that the risk of harm is low for the majority of patients at long-term dosages of ≤5 mg prednisone equivalent per day, whereas at dosages of >10 mg/day the risk of harm is elevated. At dosages between >5 and ≤10 mg/day, patient-specific characteristics (protective and risk factors) determine the risk of harm. The level of harm of glucocorticoids depends on both dose and patient-specific parameters. General and glucocorticoid-associated risk factors and protective factors such as a healthy lifestyle should be taken into account when evaluating the actual and future risk.

To cite: Strehl C, Bijlsma JWJ, de Wit M, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2015-208916

INTRODUCTION

Several guidelines and recommendations on the management of glucocorticoid therapy in rheumatology exist,[1–6] but their implementation is hampered by persisting uncertainty about the actual benefit–risk balance. Despite convincing evidence that low-dose glucocorticoids can be beneficial in rheumatoid arthritis[7–10] and other rheumatic diseases, fear of harm categorises patients and physicians as glucocorticoid 'supporters', 'opponents' or 'neutrals' (not favouring a pro or con position).[3 11–16] On the background of the known beneficial effects of glucocorticoids,[17–20] the aim of this Task Force was to achieve consensus on specific conditions where long-term glucocorticoid therapy has an acceptably low risk of harm in the treatment of chronic inflammatory rheumatic diseases. Achieving consensus is considered an essential first step towards a better implementation of existing recommendations among professionals and patients with rheumatic conditions.

METHODS

The Task Force comprised rheumatologists, epidemiologists, an endocrinologist, an infection disease specialist, a pharmacist, health professionals, four patients with rheumatic diseases and a fellow in charge of literature research. They were assigned to four breakout groups, each including at least one supporter, opponent, 'neutral', health professional and patient, respectively, focusing on the four most worrisome glucocorticoid adverse effects: osteoporosis, hyperglycaemia/diabetes mellitus (DM), cardiovascular diseases (CVDs) and infections (according to ref. [21]; see online supplementary table S1).

Systematic literature search

Prior to the group meeting, a systematic literature review was performed (see online supplementary text).

Expert discussion

The meeting started with an overview of the results of the search (see online supplementary figure S1 and tables S2–S6). After individual group discussion, the relevant evidence was summarised and presented to the whole group according to a

structured questionnaire for final discussion and consensus (see online supplementary box S1).

RESULTS

Risks of long-term glucocorticoid therapy are defined by both drug-specific (dose, duration) and patient-specific characteristics

On the background of a general agreement with current guidelines stating there is convincing evidence for the beneficial effects of low-dose glucocorticoids, the Task Force reviewed and discussed the harms of glucocorticoids. Studies on harm are often of low quality: observational designs with high risk of bias (especially confounding by indication), poor documentation of glucocorticoid exposure and differing models of risk attribution. Moreover, clinical trials of glucocorticoids have often been small, short and with limited assessment of adverse events. Consequently, results can be contradictory and their interpretation is sometimes biased (supporters may trivialise and opponents may overvalue harm). There was also consensus for the term 'long-term glucocorticoid usage' to refer to (3-) 6 months or more, based on information on glucocorticoid-induced osteoporosis.[22–24]

After critical appraisal of available evidence, the group agreed on the following statements on long-term glucocorticoid therapy in chronic inflammatory rheumatic diseases (with the exception of, eg, patients with a poor or absent response to glucocorticoids in terms of both therapeutic and adverse effects due to (partial) signalling-dependent glucocorticoid resistance[25]) (figure 1A).

- At ≤5 mg/day, there is an acceptably low level of harm for the specified outcomes (with the exception of patients at high risk for CVD who may require preventive measures).
- At >10 mg/day, the risk of harm is elevated.
- At dosages between >5 and ≤10 mg/day, uncertainty still exists and, consequently, patient-specific characteristics need particular consideration to interpret and estimate the individual risk of harm.

The actual risk of harm is patient-specific, that is, it depends on individual risk factors and/or preventive measures

Certain factors may increase the susceptibility to specific diseases in general, even without glucocorticoid exposure. For example, elderly people have an increased incidence of adverse events, including each of the harms discussed here. Also, smoking, high alcohol consumption or bad nutrition negatively influences individual health. The person can minimise these risks of harm by adopting a healthier lifestyle (including healthy nutrition and appropriate exercise).

Long-term glucocorticoid therapy potentially represents an additional risk factor, and, therefore, the glucocorticoid-associated risk of harm is patient-specific. As a general rule, early diagnosis, low disease activity, low cumulative glucocorticoid dosage, and monitoring and treatment of additional risk factors and comorbidities reduce the glucocorticoid-associated risk of harm[26–30] (figure 1B). Comprehensive information on glucocorticoid treatment is essential, and risks should be discussed with patients (and their family and/or carers, including healthcare professionals) before glucocorticoid therapy is started.[1 2]

Risk factors for osteoporosis

Glucocorticoid treatment can lead to rapid loss of bone mineral density and bone quality, and to an increased fracture risk.[26] Elderly patients receiving long-term glucocorticoid therapy have an increased risk for osteoporosis.[23 31] Additional risk factors for osteoporosis include female sex, low body weight, low bone mineral density, prevalent fractures and a family history of osteoporosis (figure 1C).[23 26 32–37] Patients can reduce their risk, for example, by appropriate exercise; glucocorticoid therapy may also support this by reducing disease activity, allowing patients to become more physically active. Guidelines also recommend sufficient vitamin D/calcium intake and treatment with bisphosphonates, osteoanabolic drugs or selective oestrogen receptor modulators (on indication)[36 38–42] (figure 1B).

Risk factors for infections

In the general population, age (>60 years) and male gender increase the risk of infection, and these may add to the risk conferred by glucocorticoids,[43–45] with the current glucocorticoid dose being more risk-relevant than former usage or cumulative dose.[45–47] Comorbidities such as chronic lung, heart, renal and certain neurological diseases, peripheral vascular diseases, DM, hepatitis C and leucopenia probably confer additive risks.[28 47–51] Also, patients with a history of prior serious infections are at increased risk. Screening for and/or vaccination against, for example, influenza, pneumococci or herpes zoster, is proposed.[50 52] Risk scores are useful to estimate potential risks and support clinical decision-making before the start of therapy[53] (figure 1B).

Risk factors for hyperglycaemia/DM

A genetic disposition, age and obesity as well as chronic inflammation are risk factors for the development of hyperglycaemia/DM, and glucocorticoids represent an additional factor, sometimes interacting with chronic inflammation[54–57] (figure 1C). Weight loss for obese patients, healthy diet, appropriate exercise and hydroxychloroquine as a therapeutic measure reduce the DM risk[58 59] (figure 1B).

Risk factors for glucocorticoid-induced CVD

Age, male sex, obesity, hypertension, diabetes and dyslipidaemia increase the risk for CVD. Glucocorticoid therapy may have an additional negative impact on the cardiovascular system.[29 60–71] Patients with active disease, extra-articular manifestations and positive rheumatoid factors and/or antibodies to citrullinated proteins have an increased risk regardless of therapy.[29 69 72–74] Patients with high disease activity or functional impairment both have an increase in cardiovascular mortality and are more likely to be treated with glucocorticoids.[29 61 68–70 73 74] Thus, glucocorticoid association with CVD might partly be explained by confounding by indication.

Preventive measures include healthy diet (low in saturated fat and calories), appropriate physical activity, sodium restriction and cessation of smoking.[60 70 75–78] Preventive use of statins or ACE inhibitors or other antihypertensive drugs has been recommended on indication[2 60 77] (figure 1B).

DISCUSSION

This Task Force concluded that the level of harm conveyed by long-term glucocorticoid therapy is dose-dependent with dosages of ≤5 mg/day producing an acceptably low level of harm (with the exception of patients at high CV risk), whereas at >10 mg/day the risk is elevated. There was consensus that patient-specific parameters clearly modify the actual risk of harm and that these need consideration when evaluating actual and future benefit–risk balance of long-term glucocorticoid therapy, especially at dosages between >5 and ≤10 mg/day.

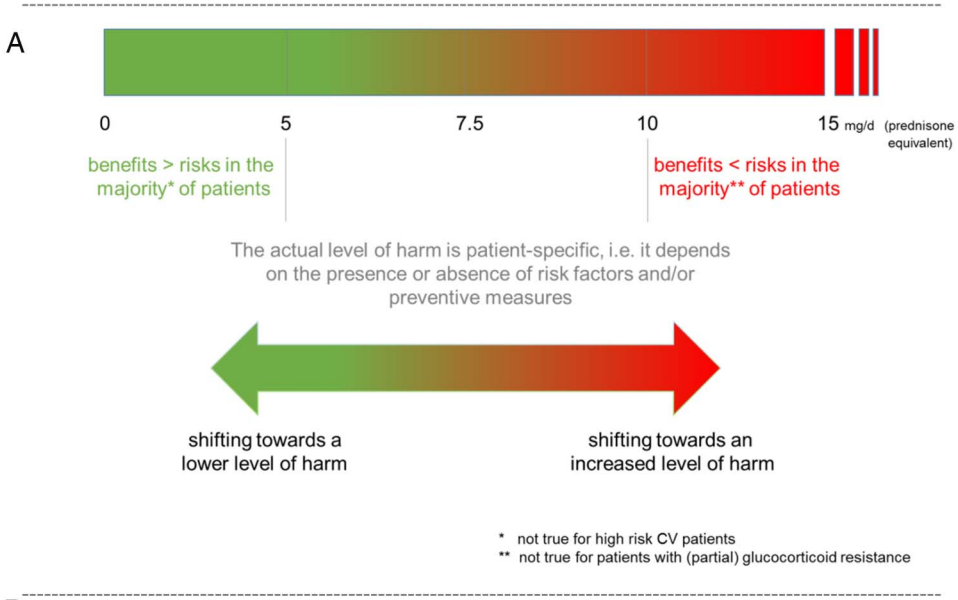

Figure 1 The level of harm of long-term glucocorticoid therapy in rheumatic diseases. Bearing in mind the beneficial effects of glucocorticoids, the Task Force members agreed that (A) at dosages of ≤5 mg/day prednisone equivalent, there is an acceptably low level of harm that is elevated at dosages of >10 mg/day. At dosages between >5 and ≤10 mg/day, there still exists uncertainty and therefore patient-specific characteristics (ie, disease activity, the presence of additional risk factors) need consideration when estimating the risk of harm. These patient-specific factors can shift the level of harm towards the (B) better or (C) worse. ACPA, anti-citrullinated peptide/protein antibodies; CV, cardiovascular; RF, rheumatoid factor.

B

Patient specific factors shifting towards a lower level of harm

	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [21] [37]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[36] [39] [40] [41] [42]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care, washing hands, good sleep)	[44] [50] [52]
Carbohydrate metabolism	healthy diet, appropriate exercise, weight loss for obese patients, prescription on indication: hydroxychloroquine, diuretics	[58] [59]
Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [60] [70] [75] [76] [77]

C

Patient specific factors shifting towards an increased level of harm

	Factors	References
General	high disease activity, high cumulative glucocorticoid dosage, lifestyle (especially bad nutrition, smoking, high alcohol consumption)	[17] [28] [66]
Glucocorticoid-induced osteoporosis	age > 60 years, female sex, low body weight, low bone mineral density, family history of osteoporosis, prevalent fractures, low calcium intake	[23] [35] [36] [37] [38]
Infections	age > 60, male sex, comorbidities (e.g. chronic lung disease, coronary heart disease, heart failure, peripheral vascular diseases, diabetes mellitus, hepatitis C, chronic renal diseases, leukopenia, neurological disease) high number of treatment failures, prior serious infections	[28] [43] [46] [47] [48] [49] [50] [51]
Carbohydrate metabolism	higher age, high body mass index, genetic predisposition, long disease duration	[54] [55]
Cardiovascular	higher age, male sex, severe extra-articular disease manifestation, RF positivity, ACPA positivity, comorbidities (e.g. hypertension, diabetes, dyslipidaemia, obesity, Cushing´s syndrome)	[29] [47] [65] [67] [72] [73] [74]

High-quality data on glucocorticoid harm are limited, and study results are often contradictory, have a high risk of bias or are evaluated inconsistently. Heterogeneous study designs (differences in glucocorticoid dosages, treatment periods, patient characteristics and total durations of therapy including former glucocorticoid usages) often lead to incomparable results and therefore sometimes contradictory conclusions. For example, a recent publication revealed that observational studies but not randomised controlled trials suggest an increased infection risk associated with glucocorticoid therapy.[46]

Box 1 Points that should be addressed in future studies

In order to improve future studies, it is necessary to unify study design and outcome parameters.
Documentation:
Gapless documentation of exact glucocorticoid dosages (including start and end date of treatment, date specific changes in dosages), day time when glucocorticoid dose is administered (eg, glucose metabolism is influenced by the circadian clock)
Harmonisation:
Glucocorticoid dosage ranges need to be reconciled
Reanalysis:
Screening of published data (eg, for adaptation of dosage ranges), analysis of unpublished data with the help of the corresponding authors
Risk scores:
Improvement, adaptation and usage of risk scores[44 48 53]
Questionnaires:
Standardisation of questionnaires and glucocorticoid-specific core outcome parameter for all clinical studies[3]

A specific conundrum refers to the 'Janus-head-like behaviour' of glucocorticoids[39 56 79]: the pro-inflammatory state of rheumatoid arthritis itself induces insulin resistance (glucocorticoids reduce the disease activity, thus counteracting this negative impact of the disease on glucose metabolism); however, glucocorticoids intrinsically also induce insulin resistance.[56] Similar scenarios exist for osteoporosis and effects on the cardiovascular system, making the impact of long-term glucocorticoid therapy a complicated study subject since exact quantification of benefits and harms is not possible with currently existing data. Consequently, patients who are uncertain about the glucocorticoid-associated risks should be thoroughly informed that an untreated disease also negatively influences other body functions. Another need is to implement existing recommendations on study design, performance, data analysis and publication, to enable future high-quality data synthesis.[3] Clearly, future study designs need improvement with regard to documentation, reproducibility and comparability (box 1).

In conclusion, the actual level of harm of long-term glucocorticoid treatment represents both a drug-specific (dose, duration) and patient-specific condition. Given the known beneficial effects of glucocorticoids, the consensus on the risks of long-term treatment achieved here represents a first step towards a better implementation of existing recommendations on glucocorticoid therapy in rheumatology. The next, ongoing step of this European League Against Rheumatism Task Force is to develop modern tools, for example, education material for patients and professionals, to achieve this goal.

Author affiliations
[1]Department of Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany
[2]Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, Utrecht, the Netherlands
[3]Amsterdam Rheumatology& Immunology Center, VU University Medical Center, Amsterdam, the Netherlands
[4]Medical Humanities, VU Medical Centre, Amsterdam, the Netherlands
[5]Department of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, the Netherlands
[6]Patient Research Partner, Mol, Belgium
[7]Department of Internal Medicine, Research Laboratory & Academic Division of Clinical Rheumatology, University of Genoa, Genova, Italy
[8]Southend University Hospital NHS Foundation Trust, Westcliff-on-Sea, Essex, UK
[9]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, University of Manchester, Manchester, UK
[10]Department of Clinical & Health Psychology, Utrecht University, Utrecht, the Netherlands
[11]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[12]Salisbury Foundation Trust NHS Hospital, Wiltshire, UK
[13]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark
[14]Epidemiology Unit, German Rheumatism Research Centre, Berlin, Germany
[15]Department of Rheumatology, Assistance Publique–Hopitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin Bicêtre, France
[16]Université Paris-Sud; INSERM U1184, Le Kremlin Bicêtre, France
[17]Faculty of Medical and Health Sciences, University of Manchester, Manchester, UK
[18]Department of Rheumatology, The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark
[19]Deutsche Reuma-Liga, Bonn, Germany
[20]Divisions of Infectious Diseases, Oregon Health & Science University, Portland, USA

Twitter Follow William Dixon at @WGDixon

Contributors We declare that all authors included on this paper fulfil the criteria of authorship.

Funding The activities of this task force are financially supported by EULAR (project number CLI073).

Competing interests JWJB reports personal fees from Mundipharma International Ltd, Horizon Pharma and Sun. MdW received consultancy fees, honoraria, travel expenses or grant support from AbbVie, Bristol-Myers Squibb GmbH & Co. KGaA, Eli-Lilly and Company, Novartis and Roche Pharma AG. MB received consultancy fees from Mundipharma International Ltd. MC received honoraria from Horizon Pharma and Mundipharma International Ltd, and grant research support from Horizon Pharma. BD reports personal fees from GSK, Servier, Mundipharma International Ltd and Sobi and grants from Napp. JL received consultancy fees from Horizon Pharma and Pfizer. HUS reports personal fees from Pfizer and Actelion and FB received consultancy fees, honoraria and travel expenses from Horizon Pharma, Pfizer and Mundipharma International Ltd, and grant support from Horizon Pharma.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Duru N, van der Goes MC, Jacobs JW, *et al*. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013;72:1905–13.
2 Hoes JN, Jacobs JW, Boers M, *et al*. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007;66:1560–7.
3 van der Goes MC, Jacobs JW, Boers M, *et al*. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis* 2010;69:1913–19.
4 Gaujoux-Viala C, Gossec L. When and for how long should glucocorticoids be used in rheumatoid arthritis? International guidelines and recommendations. *Ann N Y Acad Sci* 2014;1318:32–40.
5 Gorter SL, Bijlsma JW, Cutolo M, *et al*. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1010–14.
6 Dejaco C, Singh YP, Perel P, *et al*. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis* 2015;74:1799–807.
7 Da Silva JA, Jacobs JW, Kirwan JR, *et al*. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006;65:285–93.
8 Svensson B, Boonen A, Albertsson K, *et al*. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005;52:3360–70.
9 Bakker MF, Jacobs JW, Welsing PM, *et al*. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329–39.
10 Montecucco C, Todoerti M, Sakellariou G, *et al*. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. *Arthritis Res Ther* 2012;14:R112.
11 Neovius M, Simard JF, Askling J, *et al*. Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. *Ann Rheum Dis* 2011;70:624–9.

12 Huscher D, Thiele K, Gromnica-Ihle E, *et al*. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009;68:1119–24.
13 Ethgen O, de Lemos Esteves F, Bruyere O, *et al*. What do we know about the safety of corticosteroids in rheumatoid arthritis? *Curr Med Res Opin* 2013;29:1147–60.
14 Johannesdottir SA, Horváth-Puhó E, Dekkers OM, *et al*. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med* 2013;173:743–52.
15 Strangfeld A, Listing J, Herzer P, *et al*. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2009;301:737–44.
16 McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. *Curr Opin Rheumatol* 2008;20:131–7.
17 Saag KG, Criswell LA, Sems KM, *et al*. Low-dose corticosteroids in rheumatoid arthritis. A meta-analysis of their moderate-term effectiveness. *Arthritis Rheum* 1996;39:1818–25.
18 Thiele K, Buttgereit F, Huscher D, *et al*. Current use of glucocorticoids in patients with rheumatoid arthritis in Germany. *Arthritis Care Res* 2005;53:740–7.
19 Bazsó A, Szappanos Á, Patócs A, *et al*. The importance of glucocorticoid receptors in systemic lupus erythaematosus. A systematic review. *Autoimmun Rev* 2015;14:349–51.
20 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
21 van der Goes MC, Jacobs JW, Boers M, *et al*. Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2010;69:1015–21.
22 Rizzoli R, Biver E. Glucocorticoid-induced osteoporosis: who to treat with what agent? *Nat Rev Rheumatol* 2015;11:98–109.
23 Van Staa TP, Leufkens HG, Abenhaim L, *et al*. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:993–1000.
24 Briot K, Cortet B, Roux C, *et al*. 2014 update of recommendations on the prevention and treatment of glucocorticoid-induced osteoporosis. *Joint Bone Spine* 2014;81:493–501.
25 Wikstrom AC. Glucocorticoid action and novel mechanisms of steroid resistance: role of glucocorticoid receptor-interacting proteins for glucocorticoid responsiveness. *J Endocrinol* 2003;178:331–7.
26 van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002;13:777–87.
27 Goemaere S, Liberman UA, Adachi JD, *et al*. Incidence of nonvertebral fractures in relation to time on treatment and bone density in glucocorticoid-treated patients: a retrospective approach. *J Clin Rheumatol* 2003;9:170–5.
28 Au K, Reed G, Curtis JR, *et al*. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:785–91.
29 Myasoedova E, Crowson CS, Nicola PJ, *et al*. The influence of rheumatoid arthritis disease characteristics on heart failure. *J Rheumatol* 2011;38:1601–6.
30 Rostom S, Mengat M, Lahlou R, *et al*. Metabolic syndrome in rheumatoid arthritis: case control study. *BMC Musculoskelet Disord* 2013;14:147.
31 Tatsuno I, Sugiyama T, Suzuki S, *et al*. Age dependence of early symptomatic vertebral fracture with high-dose glucocorticoid treatment for collagen vascular diseases. *J Clin Endocrinol Metab* 2009;94:1671–7.
32 Van Staa TP, Laan RF, Barton IP, *et al*. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum* 2003;48:3224–9.
33 Kanis JA, Johansson H, Oden A, *et al*. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004;19:893–9.
34 Johansson H, Kanis JA, Odén A, *et al*. A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res* 2014;29:223–33.
35 Villa P, Moruzzi MC, Lassandro AP, *et al*. Glucocorticoid therapy as a significant risk factor for osteoporosis and fractures in an Italian postmenopausal population. *Gynecol Endocrinol* 2013;29:678–82.
36 Pereira RM, Carvalho JF, Paula AP, *et al*. Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis. *Rev Bras Reumatol* 2012;52:580–93.
37 Weinstein RS. Glucocorticoid-induced osteoporosis and osteonecrosis. *Endocrinol Metab Clin North Am* 2012;41:595–611.
38 Mitra R. Adverse effects of corticosteroids on bone metabolism: a review. *PM R* 2011;3:466–71; quiz 471.
39 van der Goes MC, Jacobs JW, Jurgens MS, *et al*. Are changes in bone mineral density different between groups of early rheumatoid arthritis patients treated according to a tight control strategy with or without prednisone if osteoporosis prophylaxis is applied? *Osteoporos Int* 2013;24:1429–36.
40 Teitelbaum SL, Seton MP, Saag KG. Should bisphosphonates be used for long-term treatment of glucocorticoid-induced osteoporosis? *Arthritis Rheu*m 2011;63:325–8.
41 Compston J. Clinical question: What is the best approach to managing glucocorticoid-induced osteoporosis? *Clin Endocrinol (Oxf)* 2011;74:547–50.
42 Mok CC, Ying KY, To CH, *et al*. Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial. *Ann Rheum Dis* 2011;70:778–84.
43 Brassard P, Lowe AM, Bernatsky S, *et al*. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis Rheum* 2009;61:300–4.
44 Crowson CS, Hoganson DD, Fitz-Gibbon PD, *et al*. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:2847–55.
45 Dixon WG, Abrahamowicz M, Beauchamp ME, *et al*. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128–33.
46 Dixon WG, Suissa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses. *Arthritis Res Ther* 2011;13:R139.
47 Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford)* 2013;52:53–61.
48 Curtis JR, Xie F, Chen L, *et al*. Use of a disease risk score to compare serious infections associated with anti-tumor necrosis factor therapy among high- versus lower-risk rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)* 2012;64:1480–9.
49 Doran MF, Crowson CS, Pond GR, *et al*. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;46:2287–93.
50 Matsumoto Y, Sada KE, Takano M, *et al*. Risk factors for infection in patients with remitted rheumatic diseases treated with glucocorticoids. *Acta Med Okayama* 2011;65:329–34.
51 Strangfeld A, Eveslage M, Schneider M, *et al*. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011;70:1914–20.
52 Winthrop KL. Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. *Rheum Dis Clin North Am* 2012;38:727–45.
53 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
54 Raul Ariza-Andraca C, Barile-Fabris LA, Frati-Munari AC, *et al*. Risk factors for steroid diabetes in rheumatic patients. *Arch Med Res* 1998;29:259–62.
55 Su CC, Chen IeC, Young FN, *et al*. Risk of diabetes in patients with rheumatoid arthritis: a 12-year retrospective cohort study. *J Rheumatol* 2013;40:1513–18.
56 Buttgereit F. Do the treatment with glucocorticoids and/or the disease itself drive the impairment in glucose metabolism in patients with rheumatoid arthritis? *Ann Rheum Dis* 2011;70:1881–3.
57 den Uyl D, van Raalte DH, Nurmohamed MT, *et al*. Metabolic effects of high-dose prednisolone treatment in early rheumatoid arthritis: balance between diabetogenic effects and inflammation reduction. *Arthritis Rheum* 2012;64:639–46.
58 Bili A, Sartorius JA, Kirchner HL, *et al*. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. *J Clin Rheumatol* 2011;17:115–20.
59 Ito S, Ogishima H, Kondo Y, *et al*. Early diagnosis and treatment of steroid-induced diabetes mellitus in patients with rheumatoid arthritis and other connective tissue diseases. *Mod Rheumatol* 2014;24:52–9.
60 Pieringer H, Pichler M. Cardiovascular morbidity and mortality in patients with rheumatoid arthritis: vascular alterations and possible clinical implications. *QJM* 2011;104:13–26.
61 Souverein PC, Berard A, Van Staa TP, *et al*. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart* 2004;90:859–65.
62 Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, *et al*. Obesity in rheumatoid arthritis. *Rheumatology (Oxford)* 2011;50:450–62.
63 Solomon DH, Curhan GC, Rimm EB, *et al*. Cardiovascular risk factors in women with and without rheumatoid arthritis. *Arthritis Rheum* 2004;50:3444–9.
64 Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. *Nat Rev Rheumatol* 2011;7:399–408.
65 Fardet L, Petersen I, Nazareth I. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. *BMJ* 2012;345:e4928.
66 Boers M, Nurmohamed MT, Doelman CJ, *et al*. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003;62:842–5.
67 Strohmayer EA, Krakoff LR. Glucocorticoids and cardiovascular risk factors. *Endocrinol Metab Clin North Am* 2011;40:409–17, x.
68 del Rincón I, Battafarano DF, Restrepo JF, *et al*. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Ann Rheum Dis* 2014;66:264–72.
69 Ajeganova S, Andersson ML, Frostegard J, *et al*. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality

depending on age at onset: a 10-year observational cohort study. *J Rheumatol* 2013;40:1958–66.
70 Soubrier M, Barber Chamoux N, Tatar Z, *et al*. Cardiovascular risk in rheumatoid arthritis. *Joint Bone Spine* 2014;81:298–302.
71 Listing J, Kekow J, Manger B, *et al*. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis* 2015;74:415–21.
72 Cambridge G, Acharya J, Cooper JA, *et al*. Antibodies to citrullinated peptides and risk of coronary heart disease. *Atherosclerosis* 2013;228:243–6.
73 Davis JM III, Maradit Kremers H, Crowson CS, *et al*. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2007;56:820–30.
74 Turesson C, McClelland RL, Christianson TJ, *et al*. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:70–5.
75 Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002;288:2569–78.
76 Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, *et al*. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73:748–51.
77 Peters MJ, Symmons DP, McCarey D, *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
78 Negri E, La Vecchia C, D'Avanzo B, *et al*. Acute myocardial infarction: association with time since stopping smoking in Italy. GISSI-EFRIM Investigators. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto. Epidemiologia dei Fattori di Rischio dell'Infarto Miocardico. *J Epidemiol Community Health* 1994;48:129–33.
79 Buttgereit F, Burmester GR, Lipworth BJ. Inflammation, glucocorticoids and risk of cardiovascular disease. *Nat Clin Pract Rheumatol* 2009;5:18–9.

Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force

Cindy Strehl, Johannes W J Bijlsma, Maarten de Wit, Maarten Boers, Nele Caeyers, Maurizio Cutolo, Bhaskar Dasgupta, William G Dixon, Rinie Geenen, Tom W J Huizinga, Alison Kent, Annette Ladefoged de Thurah, Joachim Listing, Xavier Mariette, David W Ray, Hans U Scherer, Raphaèle Seror, Cornelia M Spies, Simon Tarp, Dieter Wiek, Kevin L Winthrop and Frank Buttgereit

Ann Rheum Dis published online March 1, 2016