Συνεδρία για τα Γλυκοκορτικοειδή

Ανδρέας Γ. Μπούνας

ΕΠΕΜΥ-Καλαμάτα

24-27 Ιουνίου 2021

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Antiinflammatory Action of Glucocorticoids — New Mechanisms for Old Drugs

Turk Rhen, Ph.D., and John A. Cidlowski, Ph.D.

INFLAMMATION IS A REFLEXIVE RESPONSE TO INFECTION, THE BINDING of antibodies to antigens within the body, mechanical irritation, or injury.[1] Microbes that breach epithelial barriers, for instance, directly activate complement and toll-like receptors, two principal components of the innate immune system. The activation of these sentinels triggers the synthesis and release of inflammatory mediators with acute effects on the vasculature. Localized vasodilation, increased vascular permeability, extravasation of plasma (and humoral) proteins, and migration of leukocytes into the affected tissue produce the classic signs of inflammation: calor, dolor, rubor, tumor, and functio laesa. A positive feedback loop initiates the production of additional inflammatory cytokines once infiltrating leukocytes become activated. Antiinflammatory homeostatic mechanisms reverse these processes as the infectious agent is cleared by the innate and adaptive immune systems. The hypothalamic–pituitary–adrenal axis and glucocorticoids in particular are essential in limiting and resolving the inflammatory process.[2]

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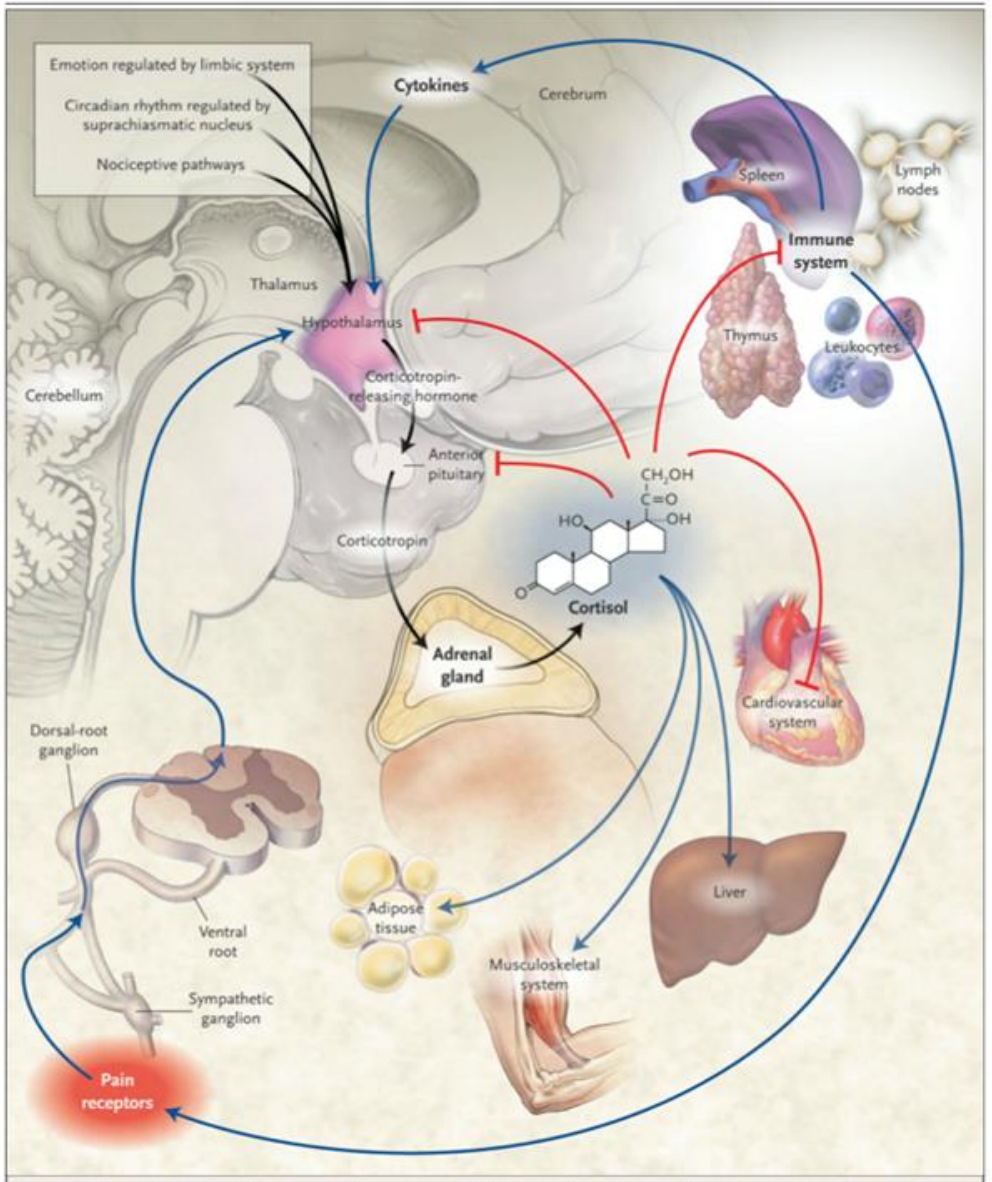
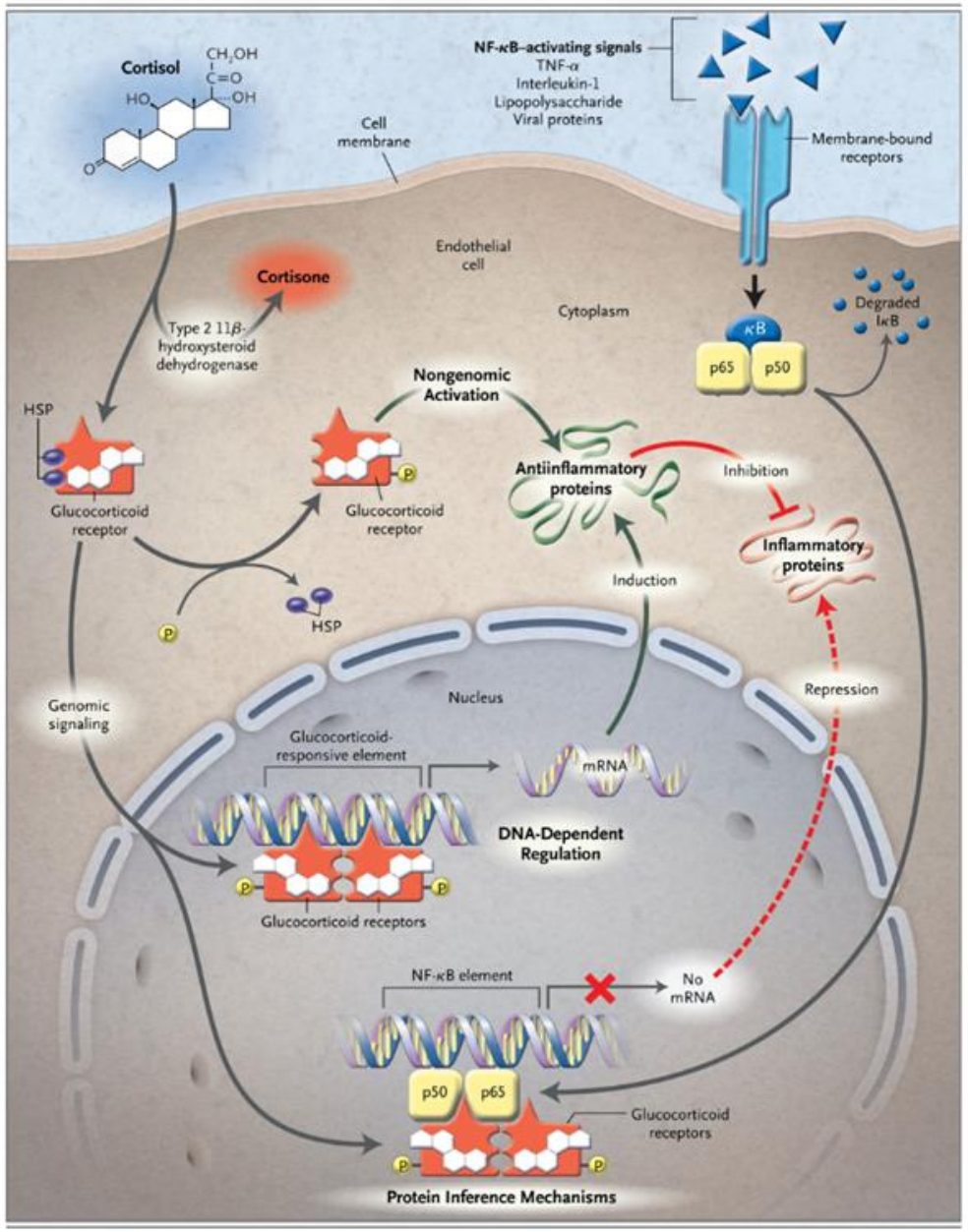


Figure 1. Pathways of Communication among the Immune System, the Hypothalamic–Pituitary–Adrenal Axis, and Other Tissues Influenced by Immune Signals and Glucocorticoids.

The diagram also shows other important influences on the hypothalamic–pituitary–adrenal axis. Red lines denote inhibition, and blue and black arrows activation.


Cortisol
NF-κB–activating signals
TNF-α
Interleukin-1
Lipopolysaccharide
Viral proteins
Membrane-bound receptors
Cell membrane
Endothelial cell
Cortisone
Cytoplasm
Degraded IκB
Type 2 11β-hydroxysteroid dehydrogenase
κB
p65
p50
Nongenomic Activation
HSP
Glucocorticoid receptor
Antiinflammatory proteins
Inhibition
Inflammatory proteins
Induction
Nucleus
Genomic signaling
Repression
Glucocorticoid-responsive element
mRNA
DNA-Dependent Regulation
Glucocorticoid receptors
NF-κB element
No mRNA
Protein Inference Mechanisms

1950: Mrs. G Gets Compound E – Mayo Clinic Researchers Receive Nobel Prize

After years of collaborative research, a Mayo Clinic team was the first to isolate cortisone, a hormone from the adrenal glands. They administered it to a patient in 1948 – and received a Nobel Prize for their discovery just two years later. Cortisone is an iconic example of Mayo's philosophy of going from "bench to bedside" – translating laboratory discoveries into effective treatments for patients.

The two Mayo Clinic staff members, rheumatologist Dr. Philip S. Hench and biochemist Dr. Edward C. Kendall, shared the 1950 Nobel Prize for Medicine or Physiology for their co-discovery of the structure and biology of cortisone, along with a Polish-Swiss chemist, Professor Tadeus Reichstein of the University of Basel. Dr. Kendall had already achieved international recognition for isolating another hormone, from the thyroid, in 1914.

The adrenal glands are small, triangular-shaped glands that sit atop each kidney. Researchers in the early 20th century studied their potential for treating inflammatory diseases such as rheumatoid arthritis. In this common, chronic and painfully debilitating disease, the body's immune system mistakenly attacks the body's joints.

Relief of pain

The Mayo team's laboratory discovery gained speed on Sept. 4, 1948, when Dr. Hench wrote to Merck & Co, Inc., manufacturers of a Mayo experimental compound. He asked for permission to administer what researchers called "Compound E" to a patient with rheumatoid arthritis in the hope of relieving her disabling pain and impaired movement.

Permission was granted. On Sept. 21, Dr. Hench and his colleague Dr. Charles H. Slocumb administered 100 mg of the adrenal gland corticosterone Compound E to the 29-year-old patient known as Mrs. G. This was the first use of the substance in history. Results were dramatic. By the third day, only few symptoms remained. Dr. Hench coined the term "cortisone" to describe the active agent in Compound E. More patients and positive results followed, along with increasing refinement of standards for administering the drug and controlling its side effects.

Mayo Clinic rheumatologist Dr. Howard F. Polley had medical responsibility for most of the patients in the initial trial of cortisone, capably assisted at Saint Marys Hospital by Sister Pantaleon Navratil, who served as nursing supervisor. In the team culture of Mayo Clinic, Dr. Hench shared the money he received as part of his Nobel Prize with colleagues who worked with him on the project. Because of her vow of poverty, Sister Pantaleon could not accept such a gift. Dr. Hench described Sister Pantaleon as "my valuable colleague" and, ever-resourceful, established a travel fund for her to visit Europe and have an audience with the Pope.

The Nobel Prize ceremony in Stockholm, Sweden, was a memorable event for Drs. Kendall

1950: Nobel Prize for discovery of cortisone

Drs. Edward Kendall (left), a laboratory scientist, and Philip Hench (right), a rheumatologist,

1955 Arthur Nobile (…..→*Corynebacterium simplex*)

Cortisone → Prednisone

Hydrocortisone (Cortisol) →Prednisolone

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72

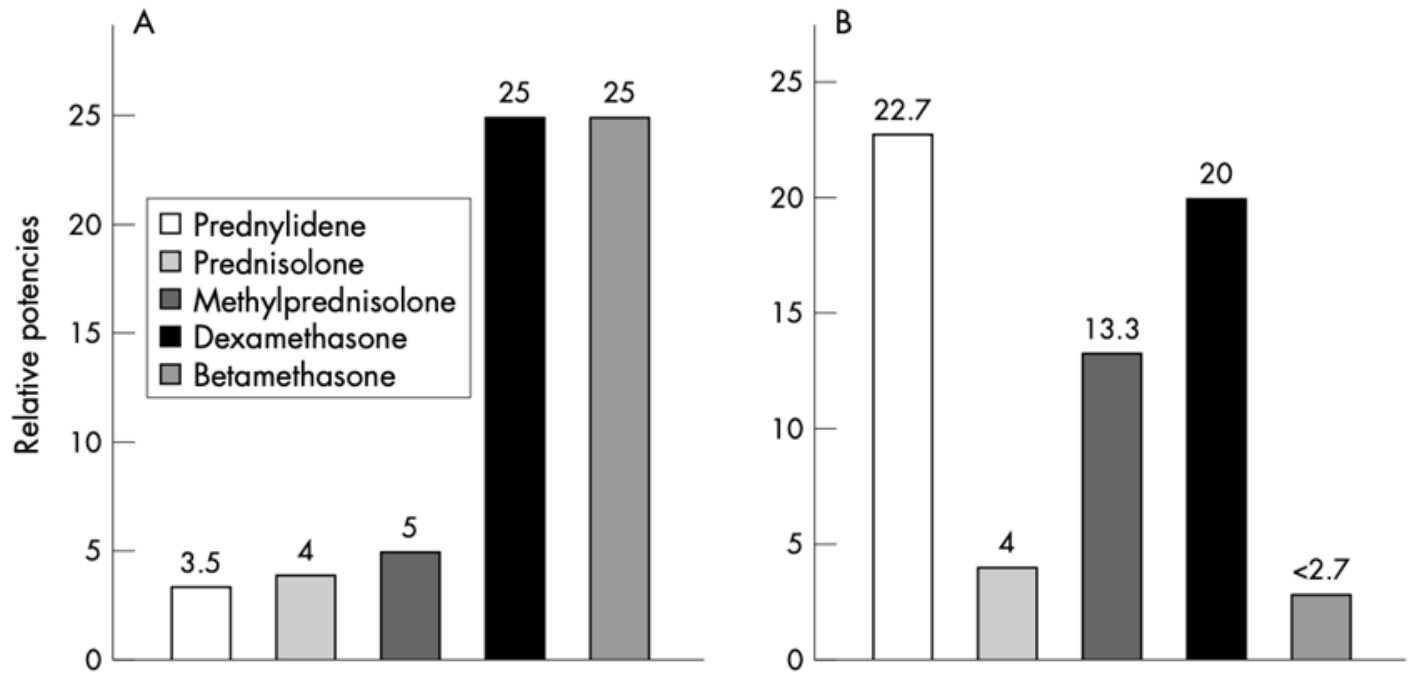


Figure 1 Relative potencies of various glucocorticoids to produce genomic and non-specific non-genomic effects. The figure shows a comparison between genomic and non-genomic potencies of various glucocorticoids. (A) Data for classic (genomic) effects were taken from Goodman and Gilman[6] and are relative to cortisol. (B) Data for non-specific non-genomic effects were taken from Schmid *et al*[8] and are relative to prednisolone. The value for prednisolone was set to 4 and values for the other glucocorticoids were scaled accordingly to allow direct comparison with the classic potencies. It should be noted that non-specific non-genomic effects are especially relevant in higher doses.

anti-inflammation is the therapeutically desired effect. In humans, hydrocortisone (cortisol) is the main glucocorticoid, and aldosterone is the main mineralocorticoid.[6] Glucocorticoids in therapeutic use for anti-inflammatory and immunosuppressive effects are nowadays exclusively synthetic molecules that have pronounced anti-inflammatory potencies compared to relative weak or even zero Na^+ retaining potencies.

usable for daily clinical work in terms of **general therapeutic guidelines**, but their dogmatic use should be avoided. We suggest therefore that (1) these values continue to be used until more exact data are available and (2) doses of different glucocorticoids are expressed by converting them into doses of "prednisone equivalent"; in other words to express doses of different glucocorticoids in mg prednisone (=mg prednisolone, as prednisone is equally as potent as prednisolone)

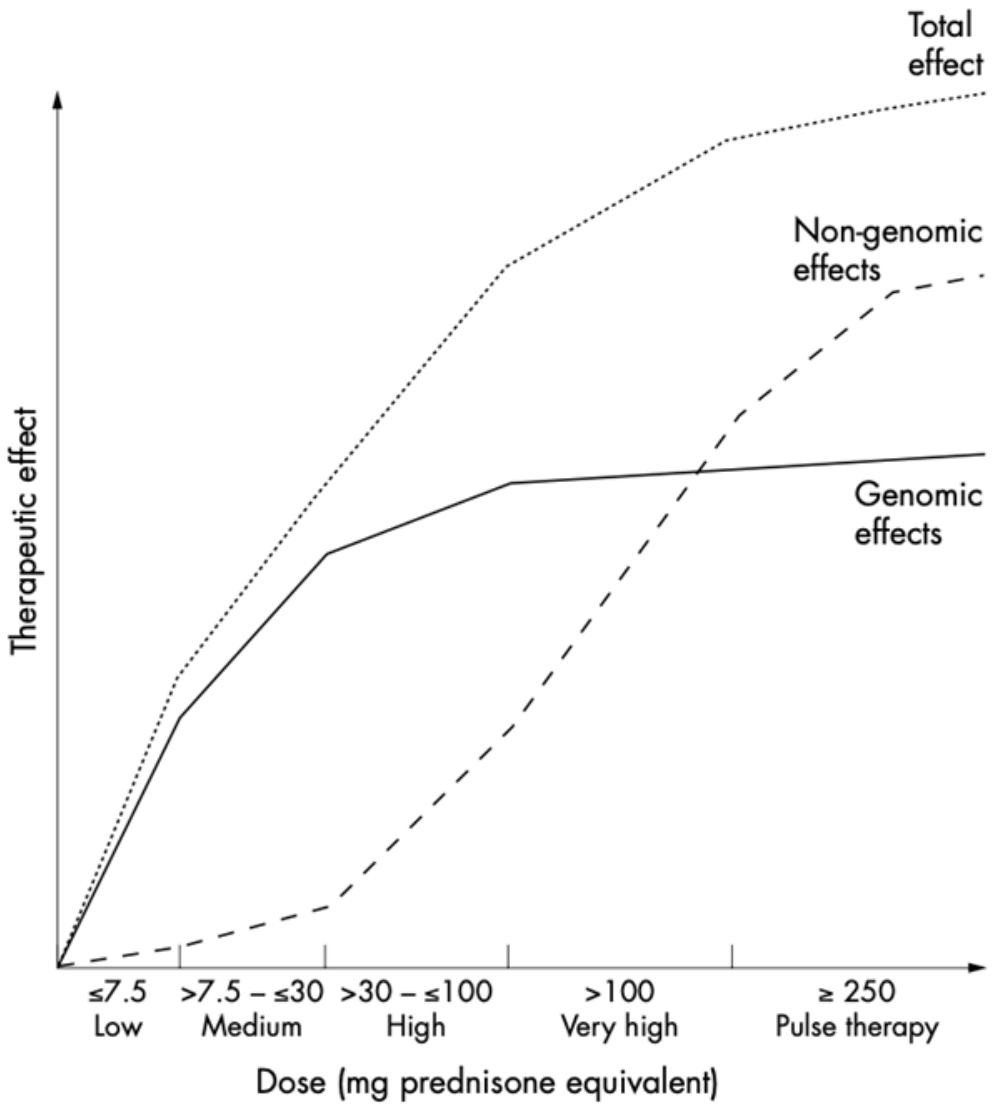


Figure 2 Current view on the dose dependency of genomic and non-genomic effects providing arguments for the description of

Note that (1) each period of glucocorticoid treatment ("treatment schedule") should be described in these terms, and (2) "tapering" the dose is a frequent procedure either to approach the maintenance dose or to stop the glucocorticoid therapy.

Cumulative dose

Many adverse effects of glucocorticoid treatment (such as glucose intolerance and osteoporosis) are related to cumulative tissue exposure. We therefore suggest describing the cumulative dose, especially in long term therapy. Currently the calculation of cumulative doses is used rather for scientific reasons.

In summary, we suggest that an appropriate description of a given glucocorticoid therapy regimen should follow this example:

Initially x mg prednisone orally once a day (at 8 00 am) for two weeks, then reduced to y mg prednisone a day, followed by . . .(describe each step of reduction in terms of mg and time) reaching zero after for example, one year (overall duration). The cumulative dose was z mg prednisone.

WHAT SHOULD BE THE DEFINITION OF CONVENTIONAL TERMS FOR GLUCOCORTICOID DOSES?

Answer

We suggest the following terminology:

- Low dose ⩽7.5 mg prednisone equivalent a day

EXTENDED REPORT

Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology

F Buttgereit, J A P da Silva, M Boers, G-R Burmester, M Cutolo, J Jacobs, J Kirwan, L Köhler, P van Riel, T Vischer, J W J Bijlsma

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In rheumatology and other medical specialties there is a discrepancy between the widespread use and the imprecise designation of glucocorticoid treatment regimens. Verbal descriptions of glucocorticoid treatment regimens used in various phases of diseases vary between countries and institutions. Given this background, a workshop under the auspices of the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials was held to discuss this issue and to seek a consensus on nomenclature for glucocorticoid treatment. This report summarises the panel's discussion and recognises that answers derived from consensus conferences are not definitive. Nevertheless, recommendations on glucocorticoid treatment are presented that (1) reflect current and best knowledge available and (2) take into account current clinical practice. A question-answer rationale presentation style has been chosen to convey the messages, to summarise the meeting in a readable format, and to avoid dogmatism.

Glucocorticoids have profound anti-inflammatory and immunosuppressive actions when used therapeutically. The therapeutic dose is very wide and depends on the indication for treatment, but can vary more than 200-fold. Clearly, different dosages and dosing regimens have distinct

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cally relevant effects mediated by genomic and
nic actions. Genomic actions involve the binding to
lucocorticoid receptors, occur at any therapeutically
sage, and are seen not earlier than 30 minutes after
nding. In contrast, non-genomic actions are medi-
ological membranes, and are seen at higher concen-
d within seconds or minutes (see below). However,
or the use of different dosages in different clinical
is essentially empirical as the evidence to support
s in specific clinical settings is very scarce. This is
by the discrepancy between the widespread use
mprecise designation of glucocorticoid treatment
in rheumatology, as in other medical specialties.
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mild to moderate, moderate, high, very high, ultra-
megadoses) and by the great variation in interpret-
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WHAT TERM SHOULD BE USED TO DESCRIBE THIS CLASS OF DRUGS (STEROIDS, CORTICOSTEROIDS, CORTICOIDS, GLUCOCORTICOSTEROIDS, GLUCOCORTICOIDS)?

Answer

We suggest the use of the term **glucocorticoids**.

Rationale

The term **steroids** is too broad as it simply describes chemical compounds characterised by a common multiple ring structure that include molecules such as cholesterol, sex hormones, and corticosteroids. The terms **corticosteroids** and **corticoids** are insufficiently exact as the adrenal cortex synthesises two classes of steroids: the **corticosteroids** in the narrower sense, which have 21 carbon atoms, and androgens, which have 19 carbon atoms. The adrenal corticosteroids in

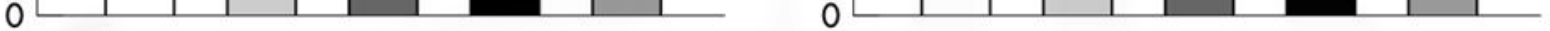
regimens used in various indications and phases of diseases varies between countries and institutions. The current terminological confusion is exemplified by the different interpretations of the various terms used to describe dosage (very low, low, mild, mild to moderate, moderate, high, very high, ultra-high, and megadoses) and by the great variation in interpretation of the terms "low dose therapy", "high dose therapy", and "pulse therapy". A clarification of this situation is needed, firstly, for scientific conciseness in clinical terms to compare trials and, secondly, because glucocorticoid actions are strongly dose dependent in both a quantitative and qualitative manner.[1 2] Moreover, it should be noted that there is currently a renewed interest in glucocorticoids based on studies describing their disease modifying effects in rheumatoid arthritis.[3–5]

Given this background, a workshop was held to discuss this issue and to seek a consensus on nomenclature for glucocorticoid treatment. A panel of experts was convened under the auspices of the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials. The panel comprised rheumatologists from Germany, the United King-

Rationale

The term **steroids** is too broad as it simply describes chemical compounds characterised by a common multiple ring structure that include molecules such as cholesterol, sex hormones, and corticosteroids. The terms **corticosteroids** and **corticoids** are insufficiently exact as the adrenal cortex synthesises two classes of steroids: the **corticosteroids** in the narrower sense, which have 21 carbon atoms, and androgens, which have 19 carbon atoms. The adrenal corticosteroids in the narrower sense differ in their relative glucocorticoid (carbohydrate metabolism regulating) and mineralocorticoid (electrolyte balance regulating) activity and were, therefore, historically described as **glucocorticoids** and mineralocorticoids.[6] Corticosteroids are grouped according to their relative potencies in Na^+ retention, effects on carbohydrate metabolism (hepatic deposition of glycogen and glucogenesis), and anti-inflammatory effects.[6] Potencies based on effects on glucose metabolism (but not effects on Na^+ retention!) closely parallel those for anti-inflammatory effects. This was the reason for using the term glucocorticoids where

Figure 1 Relative potencies of various glucocorticoids to produce



especially relevant in higher doses.

anti-inflammation is the therapeutically desired effect. In humans, hydrocortisone (cortisol) is the main glucocorticoid, and aldosterone is the main mineralocorticoid.[6] Glucocorticoids in therapeutic use for anti-inflammatory and immunosuppressive effects are nowadays exclusively synthetic molecules that have pronounced anti-inflammatory potencies compared to relative weak or even zero Na^+ retaining potencies.

For these reasons the terms **glucocorticoid(s)** or **glucocorticosteroid(s)** are scientifically correct and appropriate to describe the use of these drugs for the treatment of rheumatic diseases and other conditions where anti-inflammatory and immunomodulatory effects are desired. However, the term "glucocorticosteroids" is not very often used (only 368 citations in Medline 1994–2000) compared to the term "glucocorticoids" (11 178 citations). In summary, we suggest generally the use of the term **glucocorticoid(s)**.

HOW CAN GLUCOCORTICOID THERAPY SCHEDULES BE DESCRIBED AS PRECISELY AS POSSIBLE?

Answer

We suggest a description that is precise regarding (*a*) the drug, (*b*) the dosage, (*c*) the route of administration, and (*d*) the timing of administration (timing, frequency, duration, sometimes cumulative dosage where appropriate).

usable for daily clinical work in terms of **general therapeutic guidelines**, but their dogmatic use should be avoided. We suggest therefore that (1) these values continue to be used until more exact data are available and (2) doses of different glucocorticoids are expressed by converting them into doses of "prednisone equivalent"; in other words to express doses of different glucocorticoids in mg prednisone (=mg prednisolone, as prednisone is equally as potent as prednisolone) by using the relative potencies given above. The suggestion for further using the term prednisone equivalent is recommended for historical reasons because prednisone was the first synthetic, pharmacologically relevant glucocorticoid drug to be introduced into clinical medicine.

However, (1) It should be noted that the use of equivalent dosages is according to recent data only a valid procedure if doses of less than 100 mg prednisone are considered. At higher doses non-genomic effects come into play. This is important because the relative potencies of different glucocorticoids producing these non-genomic effects are completely different from their classic genomic effects.[2 8 9] Figure 1B shows the data that rationalise the empirical use of glucocorticoids for high dose therapy. For instance, for pulse therapy methylprednisolone is often preferred to prednisolone in exacerbated immunologically mediated disorders. The two drugs have similar genomic potency but in high dose therapy the non-specific non-genomic effect of methylprednisolone is more than threefold stronger. This may explain the empirical clinical preference for methylprednisolone. Another example

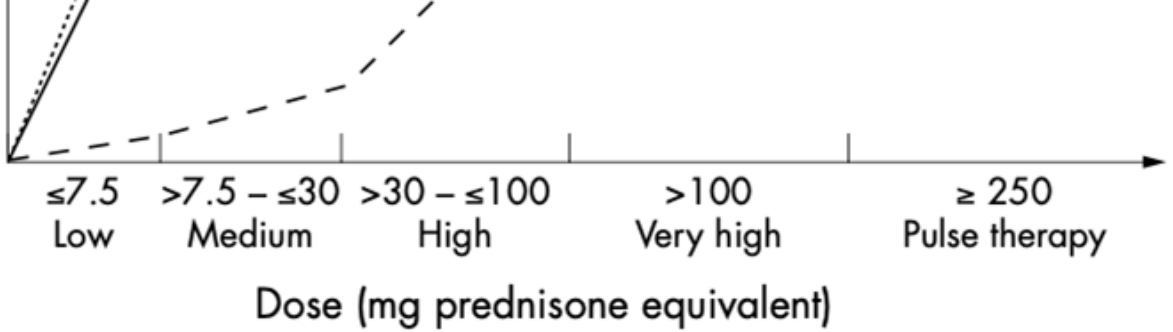


Figure 2 Current view on the dose dependency of genomic and non-genomic effects providing arguments for the description of glucocorticoid dosages. Figure 2 summarises the current knowledge on the occurrence of genomic and non-genomic effects in terms of a dose-response relationship.[1 2 6–10] This provided the basis for our recommendations on how to describe glucocorticoid doses; however, arguments concerning clinical feasibility have been taken into account. Against this background we stress that neither for genomic nor for non-genomic effects is there an exact knowledge of the relationship between dosage, concentration, and cellular and clinical effects (see text). However, this figure represents the result of our interpretation of currently available information on basic research results and clinical practice.

concentrations are reached that can, in addition to the most important genomic effects, also exert non-genomic effects. It should be noted that the range of glucocorticoids available for intra-articular administration is larger than the range for systemic use. Moreover, these intra-articular glucocorticoids differ significantly in structure with important consequences on their therapeutic effects.

tion). The cumulative dose was z mg prednisone.

WHAT SHOULD BE THE DEFINITION OF CONVENTIONAL TERMS FOR GLUCOCORTICOID DOSES?

Answer

We suggest the following terminology:

- Low dose ≤7.5 mg prednisone equivalent a day
- Medium dose >7.5 mg, but ≤30 mg prednisone equival ent a day
- High dose >30 mg, but ≤100 mg prednisone equivalen a day
- Very high dose >100 mg prednisone equivalent a day
- Pulse therapy ≥250 mg prednisone equivalent a day fo one or a few days.

Rationale

As mentioned above glucocorticoids act via genomic and non genomic effects.[1 2 7] For genomic effects the degree of cytosoli receptor saturation is considered as a direct modulator of th intensity of (therapeutic) glucocorticoid effects. Unfortu nately, there are no precise data available that describe th relationship between administered glucocorticoid dose an consequent occupation of the receptors. Moreover, it has to b taken into account that there is a wide interindividua variation in plasma concentrations where the same singl

Γλυκοκορτικοειδή=DMARDs

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extended for patients on low-dose GC therapy, except for osteoporosis (follow national guidelines), and baseline assessments of ankle edema, fasting blood glucose and risk factors for glaucoma.

Conclusion Given the incompleteness of literature data, consensus-based recommendations on monitoring for GC-related AEs were created, separately for daily practice and clinical trials.

Since their discovery, glucocorticoids (GCs) are being widely used in different diseases.[1 2] Their effects are mediated by genomic and non-genomic mechanisms.[3] GCs are beneficial in many inflammatory and rheumatic diseases, because of their anti-inflammatory and immunosuppressive actions, reducing disease activity and pain. In the long term, GCs exhibit disease-modifying capacities in rheumatoid arthritis (RA), such as protective effects on joint destruction.[4] However, their use is restrained by the occurrence of adverse events (AEs).[5–10]

Despite the established use, there is no definite consensus on the relevant AE-profile of this medication. A common misconception is that AEs important in daily practice. Currently, great efforts are being made to develop innovative GCs or GC receptor ligands that have an improved therapeutic effect/AE ratio.[15 16] So for obtaining a true AE-profile of (conventional) GCs and for comparing AEs of innovative GCs with those of conventional GCs, clear guidance and consensus on the monitoring of AEs are desirable.

The aim of this study was to develop recommendations for the monitoring of GC-related AEs of low-dose GC treatment in rheumatic diseases (1) in clinical trials for obtaining high-quality data on the occurrence of AEs and (2) in daily practice for treating patients safely. These recommendations should state *which* AEs to monitor, *how* to monitor them and *in what frequency*.

METHODS

Literature search

A review of the published evidence on GC-related AEs in rheumatic diseases was performed using the bibliographic databases PubMed, EMBASE and Cochrane Library in order to provide data for group discussions and make the recommendations as

Kirwan JR, Bijlsma JW, Boers M, *et al.* Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev* 2007;CD006356.

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

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ABSTRACT
Treatment of rheumatoid arthritis (RA) may differ among rheumatologists and currently, clear and consensual international recommendations on RA treatment are not available. In this paper recommendations for the treatment of RA with synthetic and biological disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (GCs) that also account for strategic algorithms and deal with economic aspects, are described. The recommendations are based on evidence from five systematic literature reviews (SLRs) performed for synthetic DMARDs, biological DMARDs, GCs, treatment strategies and economic issues. The SLR-derived evidence was discussed and summarised as an expert opinion in the course of a Delphi-like process. Levels of evidence, strength of

during the past decade, providing previously unforeseen therapeutic dimensions. New and highly effective DMARDs have continued to emerge until the most recent years—in particular, biological agents which target tumour necrosis factor, the interleukin 1 (IL-1) receptor, the IL-6 receptor, B lymphocytes and T-cell costimulation.[1] In addition, a chemical DMARD, leflunomide, has become available and compounds which have been in use for many decades, such as methotrexate (MTX) and sulfasalazine (SSZ), as well as GCs, have been re-examined in order to achieve better efficacy. For example, the use of high dose MTX[2] and the disease-modifying effects of GCs, especially when combined with traditional DMARDs,[3–7] are now well established. Furthermore, treatment strategies

and on the basis of its ability to increase the efficacy of biological DMARDs when used in combination,[55–59] as well as the beneficial long-term safety profile.[60] MTX is effective in DMARD naïve patients with early RA,[13 49 56 61] and its clinical efficacy has neither been surpassed by other synthetic DMARDs nor consistently by tumour necrosis factor (TNF) inhibitor monotherapy.[37 55 56 62] For these reasons the task force considered that MTX should be instituted at the earliest time point in patients with

An important fact to consider to truly appreciate the content of this recommendation, however, is that in most clinical trials comparing combination therapy with monotherapy head to head, GCs were either mandatory in the combination therapy arm or GC use was different between both arms, which probably explains the superiority of combination therapy.[74] Several other trials suggest that in the absence of GCs neither a start with combinations of synthetic DMARDs nor a step up

Recommendations

combination therapy are better than monotherapies or switching DMARDs for the major outcomes.[49 75–77] The SLR on this allowed a firm conclusion to be drawn.[18] Furthermore, in DMARD naïve patients the balance of efficacy and toxicity favours MTX monotherapy versus combination therapy, while the evidence is inconclusive in DMARD inadequate responders.[78] Therefore, the task force decided to use the word 'may' here. It is important to keep in mind that if combination therapy with synthetic DMARDs does not allow the treatment target to be achieved, it is impossible to disentangle which of the agents was insufficiently effective, precluding better

absent, could be switched to another synthetic DMARD strategy for 3–6 months before further decisions on the institution of a biological agent are taken; these other DMARDs have been mentioned in recommendation 4. However, patients for whom an initial DMARD failed and who have poor prognostic markers should have the opportunity to receive a biological DMARD in addition to their synthetic DMARD. Interestingly, closing a gap of information by using a control arm receiving active treatment, a recent study which was not part of the SLR reported that for patients with early RA who had failed to reach low disease activity after 3 months' MTX

Final set of 15 recommendations for the management of RA

1	Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
2	Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent (every 1–3 months) and strict monitoring
3	MTX should be part of the first treatment strategy in patients with active RA
4	When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ or injectable gold
5	In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
6	GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible
7	If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered
8	In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started*; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab)† which should be combined with MTX*
9	Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab

Recommendations

In each subgroup, the members discussed the evidence provided by the fellows in their SLRs in detail and agreed on five to eight recommendations for the respective topic. These preliminary statements on the management of RA with synthetic DMARDs, GCs and biological agents, as well as on treatment strategies and economic aspects, were subsequently reviewed intensively by the whole task force, synthesised and voted upon. This process led to 15 recommendations on drug management and treatment strategies. Each of these 15 recommendations was then subjected to an economic valuation in accordance with the results obtained by the economics subgroup of the task force.

The 15 recommendations (detailed in table 1) are presented in the text below in an abbreviated version. The levels of evidence and strengths of recommendation for each recommendation are then shown in table 2 and the economic valuation in table 3. The 15 recommendations are ordered by a logical sequence or procedural and chronological hierarchy rather than by any major weight of importance, with the exception of the first two points which constitute the foundation of all subsequent items. They also serve as basis for the algorithm provided in figure 1.

(1) *Synthetic DMARDs early*—The task force was unanimous in its view that in the vast majority of patients with RA the first treatment approach should include synthetic DMARDs, since a significant proportion of patients can attain a state of very low disease activity or remission[36–39]; the types of DMARD with evidence of efficacy will be discussed in items 3–6. Moreover, since

outcomes. However, studies allowing a direct comparison of GCs plus DMARD monotherapy versus GCs plus combination DMARDs have not been done.

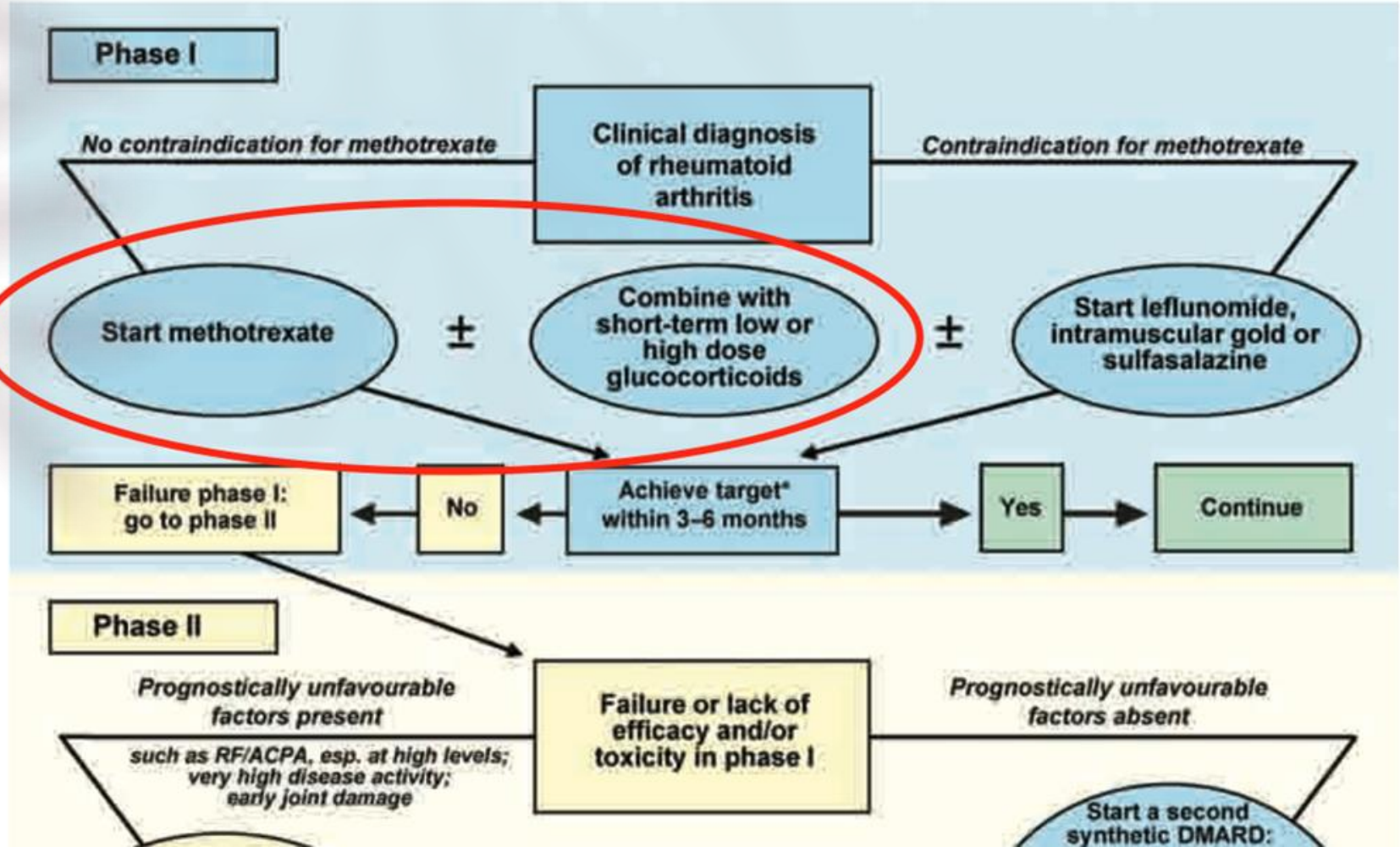
(6) *Glucocorticoids*—GCs have been shown to have not only anti-inflammatory but clearly also disease-modifying properties.[5 79 80] The evidence that DMARD monotherapy is as efficacious as DMARD combination therapy suggests that the significantly better outcomes of trials using combinations of synthetic DMARDs plus GCs versus DMARD monotherapy might be due to the GC component.[7 12 42] This notion finds important support in studies which show that adding GCs to DMARD monotherapy[3 4] is beneficial. GC treatment has been added to DMARDs successfully at low doses (<10 mg/day),[3 4 42] but more rapid improvement may be achieved by addition of GCs at higher doses for the short term.[7 49] However, the added efficacy of high-dose GCs has not yet been compared with that of low-dose GCs and, therefore, sufficient evidence for this is lacking. Importantly, long-term use of GCs can lead to adverse events,[81] but there may also be safety concerns in the intermediate term, although most studies on the toxicity of GCs are of low quality and short duration. Nevertheless, their toxicity, particularly in the intermediate to long term, should in the opinion of the task force not be disregarded and thus GCs should be used with caution and preferably for only short periods of time. Consequently, GCs should be tapered as rapidly as possible in accordance with the clinical situation. The safety of GCs was also an important aspect of the EULAR recommendations on the management of GC treatment.[82]

(7) *Addition of a biological DMARD or switch to another synthetic*

in the absence of added GCs (even triple treatment of MTX, SSZ and hydroxychloroquine) has limited efficacy and may not have higher efficacy than if the patients had been switched to SSZ, as was shown in the BeSt trial.[12] This limited (but partly exhibited) efficacy of such a synthetic DMARD regimen also supports the expert opinion of switching patients for whom a first DMARD strategy has failed and who do not have bad prognostic markers to another DMARD (or eventually DMARD combination). In contrast, for patients for whom initial MTX or other synthetic DMARDs (ideally with GCs) has failed and who have bad prognostic indicators a biological DMARD, in general, and a TNF inhibitor, in particular, should be employed. Importantly, however, no randomised controlled or observational clinical trials to date have tested this approach of differential treatment based on prognostic factors. Therefore, this statement is at the level of an expert opinion, but is supported by various indirect evidence provided in the existing literature.

(8) *Initiation of a TNF inhibitor*—This expansion of statement No 7, which applies to patients followed according to that previous statement, emphasises that biological agents are effective if synthetic DMARDs have failed (level 1a, grade A) and that they should be combined with MTX (or other DMARDs), since this combination has greater efficacy than monotherapy with most biological agents; this is well established for TNF inhibitors on the basis of respective comparative phase III trials[55 56] and for rituximab and tocilizumab on the basis of comparative phase II trials[58 59] (level 1b, grade A). At the time of the SLR, the only biological agents licensed in Europe for treating patients with RA with active disease

Recommendations



EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Ferdinand C Breedveld,[5] Maya Buch,[6,7] Gerd Burmester,[8,9] Maxime Dougados,[10] Paul Emery,[6,7] Cécile Gaujoux-Viala,[11] Laure Gossec,[12] Jackie Nam,[6,7] Sofia Ramiro,[13,14] Kevin Winthrop,[15] Maarten de Wit,[16] Daniel Aletaha,[1] Neil Betteridge,[16] Johannes W J Bijlsma,[17] Maarten Boers,[18] Frank Buttgereit,[8,9] Bernard Combe,[19] Maurizio Cutolo,[20] Nemanja Damjanov,[21] Johanna M W Hazes,[22] Marios Kouloumas,[16] Tore K Kvien,[23] Xavier Mariette,[24] Karel Pavelka,[25] Piet L C M van Riel,[26] Andrea Rubbert-Roth,[27] Marieke Scholte-Voshaar,[16] David L Scott,[28] Tuulikki Sokka-Isler,[29,30] John B Wong,[31] Désirée van der Heijde[5]

Handling editor Francis Berenbaum

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ABSTRACT

In this article, the 2010 European League against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis (RA) with synthetic and biological disease-modifying antirheumatic drugs societies and other stakeholders about EULAR's most recent consensus on the management of RA with sDMARDs, glucocorticoids and bDMARDs. They are based on evidence and expert opinion and intended to improve outcome in patients with RA.

Table 1 2013 Update of the EULAR recommendations (the table of 2010 recommendations can be seen in the online supplement or the original publication)

	Overarching principles
A.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B.	Rheumatologists are the specialists who should primarily care for RA patients
C.	RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist
	Recommendations
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2.	Treatment should be aimed at reaching a target of remission or low disease activity in every patient
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4.	MTX should be part of the first treatment strategy in patients with active RA
5.	In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy
6.	In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used
7.	Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible
8.	If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered
9.	In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX
10.	If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action
11.	Tofacitinib may be considered after biological treatment has failed
12.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering‡ bDMARDs§, especially if this treatment is combined with a csDMARD
13.	In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
14.	When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

table, while acknowledging that its efficacy remains established by high-quality evidence.[78] Further, antimalarials, such as hydroxychloroquine and chloroquine, are used in RA, especially in combination therapy, but also as monotherapy in patients with very mild disease.[79] Interestingly, beyond their mild DMARD activity, antimalarials exhibit a variety of positive metabolic effects and are also considered to be safe during pregnancy.[80 81] Because they may not retard progression of joint damage to the same extent as other agents,[65 82] they have not been mentioned more prominently in this statement, although patients with low disease activity have a low propensity for joint destruction. Finally, compared with the previous statement on these drugs, the term 'early' has now been added to 'intolerance' to indicate the Task Force's view that early intolerance to MTX (within 6 weeks) should be viewed as a contraindication and not as a failure of the first treatment strategy. Of note, the Task Force decided unanimously to delete recommendation 10, which also dealt with potential alternative therapies for desperate cases ('In the case of refractory severe RA or contraindications to biological agents or the previously mentioned sDMARDs, the following sDMARDs might be also considered, as monotherapy or in combination with some of the above: azathioprine, cyclosporine A [or exceptionally cyclophosphamide]') from the table of recommendations. Given the many currently available effective csDMARDs and bDMARDs and the view that the benefit/risk ratio of the mentioned drugs was not convincingly favourable, especially in relation to other therapies, their use in a first treatment strategy should be restricted to rare, exceptional situations (for details see 2010 recommendations).[3]

of adverse events should be considered when discussing treatment options with them. In general, combination therapy with csDMARDs should include MTX, since other combinations have not been sufficiently studied. Finally, the Task Force recognised the limitations of meta-analyses in the light of new studies[84 86] contradicting a meta-analysis that had suggested similar structural efficacy for csDMARD combinations and bDMARD treatment.[91]

7. *Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible.* As before, the Task Force heavily debated the role of glucocorticoids (previously recommendation 6). Indeed, this item was reworded (previously: 'Glucocorticoids added at low to moderately high doses to sDMARD monotherapy [or combinations of sDMARDs] provide benefit as initial short term treatment, but should be tapered as rapidly as clinically feasible.'). Rather than just making the general statement that glucocorticoids may 'provide benefit', the Task Force now recommends that they should be considered as part of the initial therapeutic approach. This change is based on the respective SLR[13] which includes additional information accrued over the last few years.[85 92] Low dose refers primarily to a dose of 7.5 mg prednisone or equivalent per day or less.[93] Mentioning glucocorticoids in a separate recommendation results from their proven capacity to increase clinical, functional and structural efficacy when combined with csDMARDs,[92 94–96] and this combination has similar efficacy when compared with TNF inhibitors plus MTX[60 97]; thus glucocorticoids, both in initially high and rapidly

rare, exceptional situations (for details see 2010 recommendations).[3]

6. *In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used.* In the previous set of recommendations, item 5 read: 'In DMARD-naïve patients, irrespective of the addition of glucocorticoids, sDMARD monotherapy rather than combination therapy of sDMARDs may be applied.' This wording expressed a preference for monotherapy based on the respective SLRs,[64 83] which had revealed no superiority of combination therapy using csDMARDs when excluding the concomitant use of glucocorticoids. However, by saying 'may', that statement did not generally oppose the use of csDMARD combination therapy; this was also reflected in the respective figure depicting the proposed algorithm. Since then, several additional studies suggest that csDMARD combination may be superior to MTX monotherapy, and some even found efficacy to be similar to that of bDMARDs.[84–88] Nevertheless, although these trials yielded similar results strengthening their interpretation, controversy persists because of methodological limitations of these studies,[13] which were also clearly stated in some of the reports themselves. Moreover, additional recent data suggest that sequential monotherapy is as effective as combination therapy in clinical, functional and structural outcomes[89 90] and that stepping up from MTX monotherapy to a biological agent has significant superiority over a combination of csDMARDs.[89] Nonetheless, the Task Force agreed unanimously that the use of csDMARD combination therapy should be mentioned as an appropriate alternative

cacy when compared with TNF inhibitors plus MTX[60 97]; thus glucocorticoids, both in initially high and rapidly tapered regimens (eg, COBRA) and at lower doses extended over a year or two, may increase DMARD activity and are even effective in this regard as monotherapy.[98 99] However, glucocorticoid monotherapy is not specifically recommended by the Task Force and should only be used in exceptional cases when all other DMARDs have contraindications. A separate EULAR committee has concluded that the literature on safety of long-term glucocorticoid therapy at low doses still has important gaps, but in general does not support the notion of unacceptable safety issues[100]; subsequently, that committee formulated management guidelines that also address preventive measures against glucocorticoid-induced adverse events.[101] The current SLRs[13 15] are not in disagreement with any of the above findings. Nevertheless, the adverse event profile and comorbidity implications of glucocorticoids (and thus their benefit/risk profile) elicited a fierce debate within the Task Force. A compromise (based on expert opinion) to be more specific with respect to the time frame of their application by stating 'up to 6 months' rather than just 'short term' ultimately led to a majority vote; however, only 73% of the members approved this item (the lowest majority level of all recommendations), reflecting divergent opinions, with both proponents of a stronger and a weaker recommendation voting against. However, the level of agreement (strength of recommendation) was quite high (mean of 8.9) upon final anonymous grading. Thus, the Task Force suggests using them only as bridging therapy and limiting their use to a maximum of 6 months, ideally tapering them at

comes and that stepping up from MTX monotherapy to a biological agent has significant superiority over a combination of csDMARDs.[89] Nonetheless, the Task Force agreed unanimously that the use of csDMARD combination therapy should be mentioned as an appropriate alternative

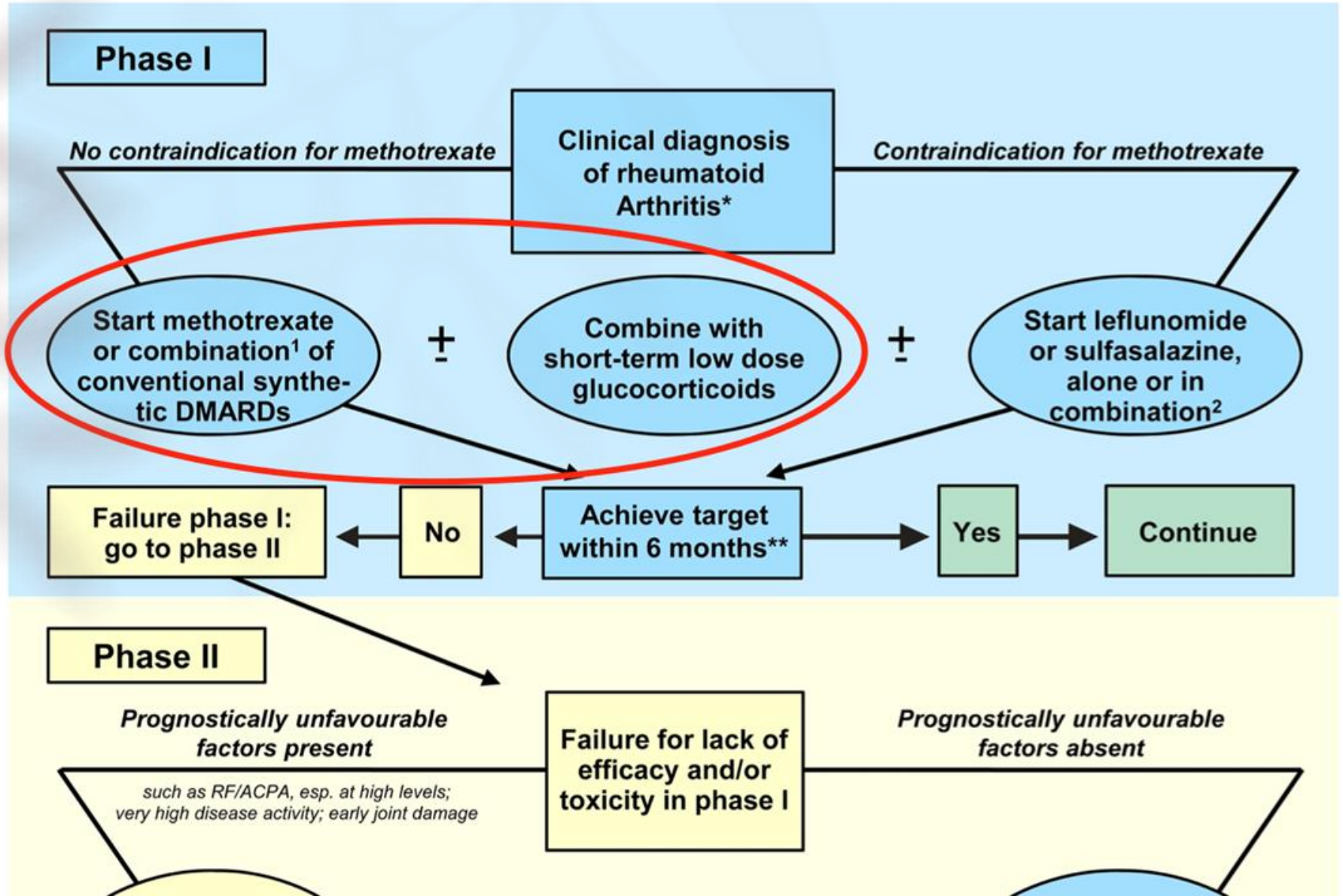
(strength of recommendation) was quite high (mean of 8.9) upon final anonymous grading. Thus, the Task Force suggests using them only as bridging therapy and limiting their use to a maximum of 6 months, ideally tapering them at

earlier time points. However, neither chronic use of glucocorticoids in established RA nor intra-articular glucocorticoid applications were discussed. Of note, it was also decided to change the algorithm in figure 1 from the 2010 version by downsizing the '–' compared with the '+' in the '±' symbol to reflect the increasing agreement of the Task Force that glucocorticoids should be combined with MTX or other csDMARD regimens.

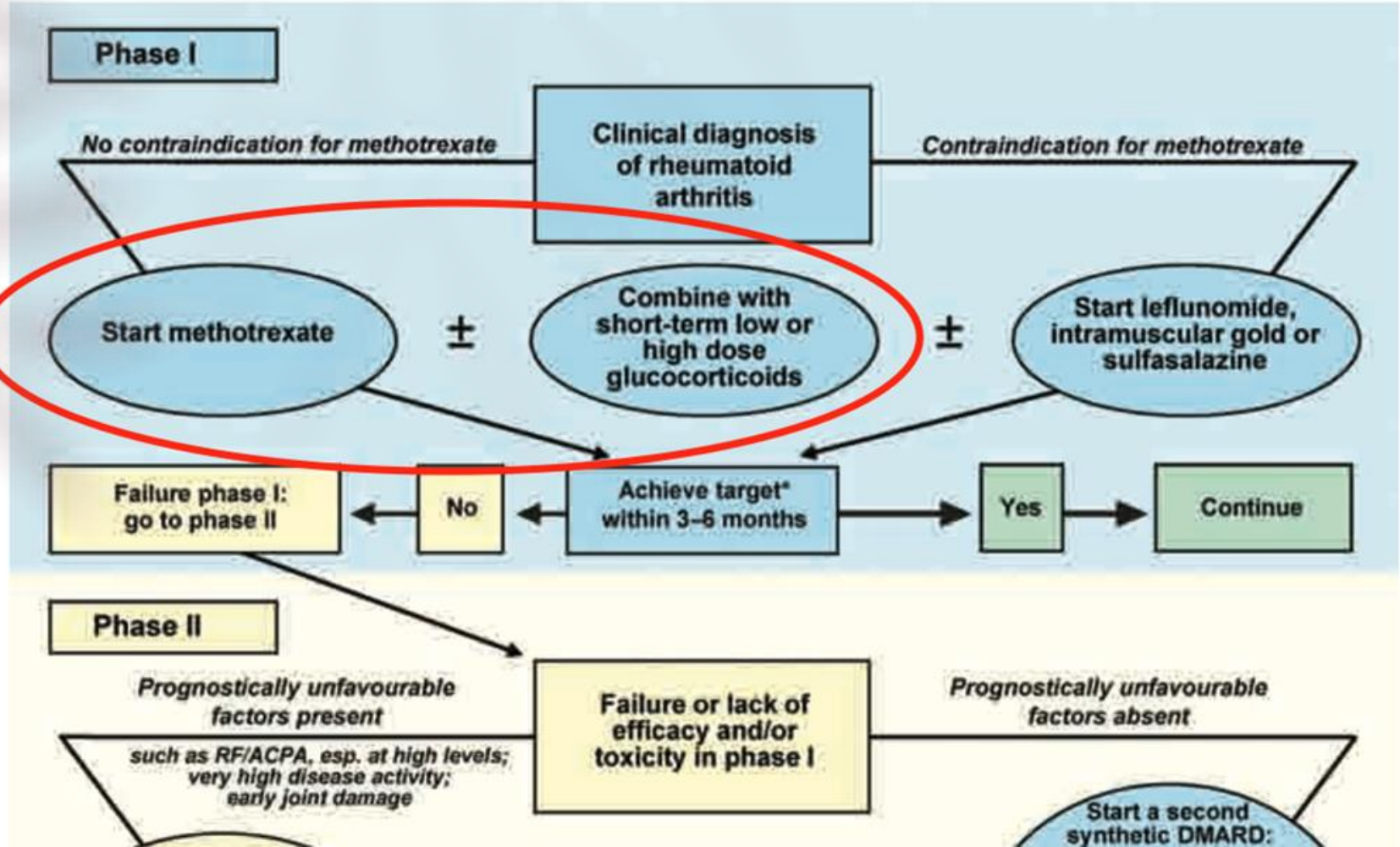
8. *If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered.* Slightly reworded compared with 2010, this statement reiterates the unanimous view of the Task Force that risk stratification is an important aspect in the therapeutic approach to RA. These risks have been well defined over the years and include a high

9. *In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors, abatacept or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX.* This point was approved as worded by 90% of the participants. First, the Task Force reiterated here that bDMARDs should primarily be started when patients did not achieve the therapeutic target after treatment with csDMARDs for 6 months (or had no improvement at 3 months). Second, it explicitly defined the agents it meant when mentioning 'biological DMARDs'. In the 2010 recommendations, the Committee had added 'current practice would be to start a TNF inhibitor', and explained this expert opinion with the long-term use of TNF blockers and the availability of registry data when compared with abatacept and tocilizumab; this was simply an expression of a preference based on their larger and longer evidence base

Recommendation



Recommendations



EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Johannes Bijlsma,[5] Gerd Burmester,[6] Katerina Chatzidionysiou,[7] Maxime Dougados,[8] Jackie Nam,[9] Sofia Ramiro,[10] Marieke Voshaar,[11] Ronald van Vollenhoven,[3,4] Daniel Aletaha,[1] Martin Aringer,[12] Maarten Boers,[13] Chris D Buckley,[14] Frank Buttgereit,[6] Vivian Bykerk,[15,16] Mario Cardiel,[17] Bernard Combe,[18] Maurizio Cutolo,[19] Yvonne van Eijk-Hustings,[20] Paul Emery,[10] Axel Finckh,[21] Cem Gabay,[21] Juan Gomez-Reino,[22] Laure Gossec,[23] Jacques-Eric Gottenberg,[24] Johanna M W Hazes,[25] Tom Huizinga,[11] Meghna Jani,[26] Dmitry Karateev,[27] Marios Kouloumas,[28,29] Tore Kvien,[30] Zhanguo Li,[31] Xavier Mariette,[32] Iain McInnes,[33] Eduardo Mysler,[34] Peter Nash,[35] Karel Pavelka,[36] Gyula Poór,[37] Christophe Richez,[38] Piet van Riel,[39] Andrea Rubbert-Roth,[40] Kenneth Saag,[41] Jose da Silva,[42] Tanja Stamm,[43] Tsutomu Takeuchi,[44] René Westhovens,[45,46] Maarten de Wit,[47] Désirée van der Heijde[10]

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ABSTRACT

patients, national rheumatology societies, hospital

Table 1 Glossary and definitions

Term	Definition	
Poor prognostic factors	▶ Moderate (after csDMARD therapy) to high disease activity according to composite measures[71] ▶ High acute phase reactant levels[72 73] ▶ High swollen joint counts[72–74] ▶ Presence of RF and/or ACPA, especially at high levels[72 75] ▶ Combinations of the above[69 76] ▶ Presence of early erosions[72] ▶ Failure of two or more csDMARDs[77]	
Low-dose glucocorticoid	▶ ≤7.5 mg/day (prednisone equivalent)[57 78]	
Meanings of treatment reduction		
Tapering	▶ Usually reduction of drug dose or increase of application interval ('spacing') ▶ May include discontinuation (tapering to 0), but then only after slow reduction	
Cessation, discontinuation	Stopping of a particular drug	
Disease activity states		
Remission	ACR-EULAR Boolean or index-based remission definition[22]	
Low disease activity	Low disease activity state according to any of the validated composite disease activity measures that include joint counts[79–81]	
Moderate, high disease activity	Respective disease activity state according to any of the validated composite disease activity measures that include joint counts[79–81]	
DMARD nomenclature[12]		
Synthetic DMARDs	▶ Conventional synthetic DMARDs (csDMARDs)	For example, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
	▶ Targeted synthetic DMARDs (tsDMARDs)	For example, tofacitinib, baricitinib
Biological DMARDs	▶ Biological originator DMARDs (boDMARDs)	
	▶ Biosimilar DMARDs (bsDMARDs)	

ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; RF

Table 2 The 2016 EULAR updated recommendations

	Overarching principles
A	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues
C	Rheumatologists are the specialists who should primarily care for patients with RA
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist
	Recommendations
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4.	MTX should be part of the first treatment strategy
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered
8.	If the treatment target is not achieved with the first csDMARD strategy, when

Table 3 Evidence levels, voting results and agreement

	LoE	SoR	Final vote (%)	Level of agreement (0–10)
A	n.a.	n.a.	100	9.9
B	n.a.	n.a.	100	9.9
C	n.a.	n.a.	100	9.8
D	n.a.	n.a.	98	9.7
1.	1a	A	96	9.9
2.	1a	A	91	9.6
3.	2b		100	9.5
4.	1a	A	71	9.8
5.	1a	A	85	9.0
6.	1a	A	98	8.7
7.	5	D	94	8.5
8.	*1b §5	*A §D	96	9.0
9.	*1a #1b	*A #A	96	9.2
10.	*1a §5	A* §D	71	9.1
11.	2b	B	86	9.0
12.	4	C	86	8.5

The symbols (*, §, #) relate to the corresponding symbols in the recommendations (table 2), showing the respective LoE.
LoE, levels of evidence; n.a., not available; SoR, strength of recommendation.

patients with very mild disease,[138] particularly in China. Interestingly, antimalarials may have significant positive effects on lipid and glucose metabolism[139] and may reduce cardiovascular risk in RA.[140] However, joint damage is not retarded to a similar extent as with other csDMARDs.[141] This recommendation also uses the term 'treatment strategy' implying, as with MTX, that leflunomide and sulfasalazine can be used as monotherapy or in combination with other csDMARDs or biological agents.[142–145] Indeed, step-up combination therapy is frequently employed, even though comparing step-up combination with switching of csDMARD did not reveal significant differences in outcomes.[146] LoE 1a; LoA 9.0.

6. *Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible*. The added efficacy of GC when combined with csDMARDs is well established. Indeed, hitherto all trials comparing GC plus csDMARD with bDMARDs plus csDMARD revealed similar efficacy.[146 147] In 2013, GC were dealt with in recommendation 7, but the wording was different: 'low-dose GC should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible'. The current wording constitutes a compromise attempting to accommodate most of the concerns and suggestions raised during the Task Force's debate.

The term 'low-dose' was critically discussed. While all members of the Task Force agreed that high doses of GC should not be used for prolonged periods, it also became clear that the label 'low-dose' (which means a daily dose of 7.5 mg or less prednisone per day),[78 148] while preferred by some Task Force Force underlines that GC should be gradually reduced and ultimately stopped, usually within 3 months from treatment start and only exceptionally by 6 months. Long-term use of GC, especially at doses above 5 mg/day, should be avoided because of the many potential risks presented in the SLR.[50 52 57] While some of these risk associations may be due to confounding by indication in patients with high disease activity,[151] the evidence for increased overall and cardiovascular mortality at a dose above a threshold of 7.5 mg/day or a cumulative dose of 40 g is considerable.[152] Of note, applying GC as a sole therapeutic change in patients with IR to csDMARD therapy does not convey good efficacy and is associated with significant adverse events.[153] Moreover, if GC cannot be withdrawn within the time frame mentioned above, the DMARD therapy may have to be considered a failure. Finally, intra-articular GC application may have to be considered in certain instances, such as a residually inflamed or a reactivated joint.

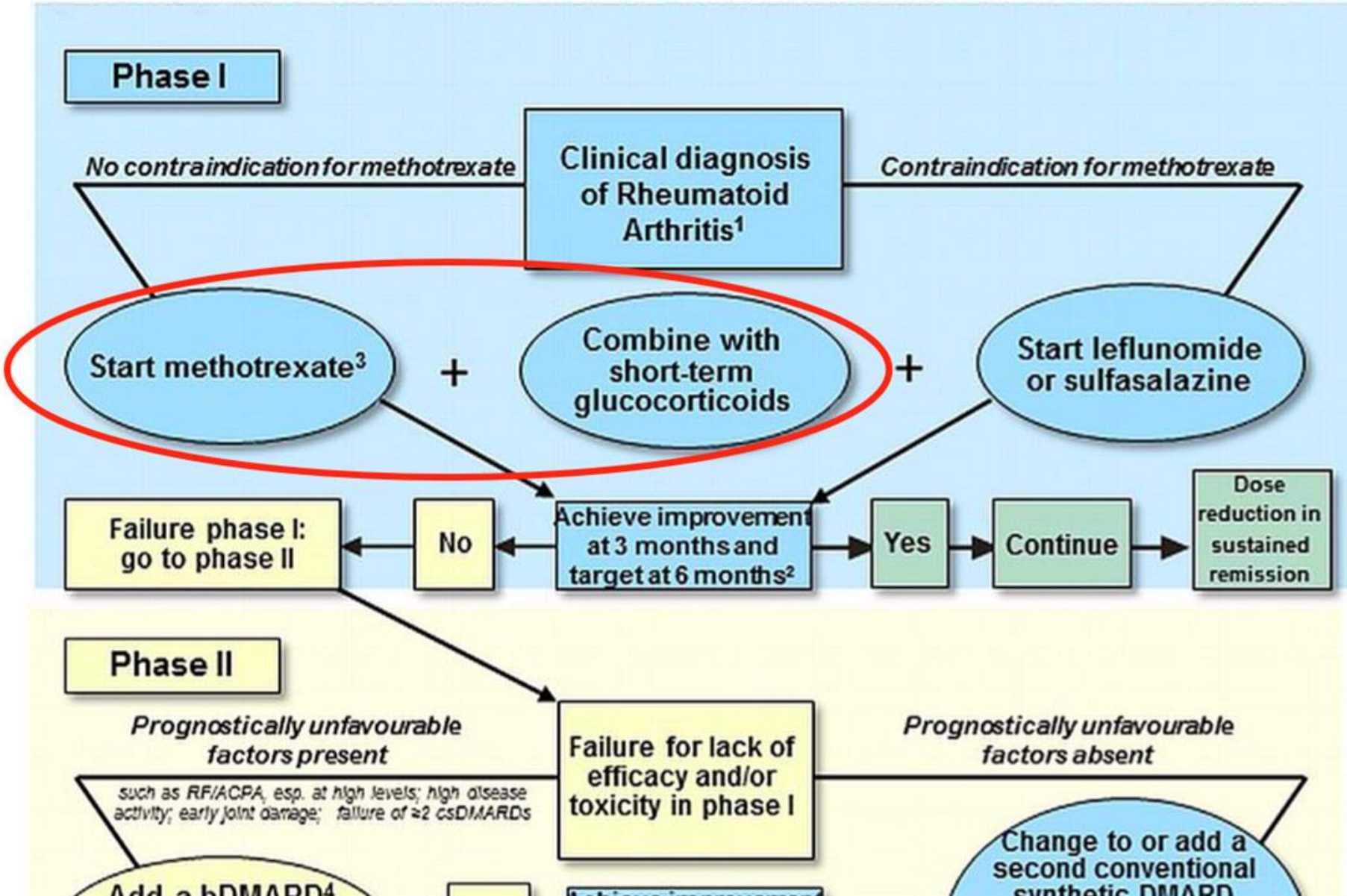
Some Task Force members advocated the chronic use of GC as a possibility for some patients; however, this proposal was not endorsed by the majority. While the bullet point on GC was, as in previous years, most heavily debated, the final wording received a 98% majority vote. However, the LoA was much lower (8.7), in line with previous versions of the recommendations. This relatively low LoA is presumably due to the fact that many Task Force members felt that this point was too liberal and the use of GC should be more restricted, while others were of the opinion that it was too restrictive. LoE 1a; LoA 8.7.

7. *If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered*. This sentence constitutes

146 Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, *et al*. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381–90.

147 Nam JL, Villeneuve E, Hensor EM, *et al*. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). *Ann Rheum Dis* 2014;73:75–85.

Recommendation



EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

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Table 1 Glossary and definitions (after[9])

Term	Definition
Poor prognostic factors	► Persistently moderate or high disease activity despite conventional synthetic DMARD (csDMARD) therapy according to composite measures including joint counts ► High acute phase reactant levels ► High swollen joint count ► Presence of RF and/or ACPA, especially at high levels ► Presence of early erosions ► Failure of two or more csDMARDs
Low-dose glucocorticoids	<7.5 mg/day (prednisone equivalent)
Tapering	► Reduction of drug dose or increase of application interval ► May include cessation (tapering to 0), but then only after slow reduction
Cessation, stopping	► Stopping of a particular drug
Disease activity states	
Remission	ACR-EULAR remission definition (Boolean or index based)
Low disease activity	Low disease activity state according to any of the validated composite disease activity measures that include joint counts
Moderate, high disease activity	Respective disease activity state according to any of the validated composite disease activity measures that include joint counts

of shared decision-making was reiterated and the importance of patient education emphasised. Indeed, patient education may increase adherence to medication[49]; moreover, education of rheumatologists may foster adherence to appropriate assessment strategies.[50] There were suggestions made to expand this item by mentioning the importance of patient education separately, but there was ultimate agreement that patient education forms the implicit and inseparable basis for shared decision-making. Nevertheless, since shared decision-making is so important, communication skills should also be a focus of rheumatologists and other health professionals. This item is also included in a publication on quality indicators that should be incorporated in the decision process.[51] It should also be noted that the focus of the task force was on DMARDs and not on other pharmacological and non-pharmacological therapies which may have to be considered in many patients as adjunctive therapies for best care. The task force agreed at a level of 9.7 (SD 1.1) with this principle.

B. *Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage*. Added in 2016 and remaining unchanged, this principle is particularly important when considering the use of bDMARDs and tsDMARDs. The higher risk of herpes zoster infections on JAK-inhibitors, more pronounced in some Asian countries such as Japan and South Korea, is captured under this principle. The prevalent

	Overarching principles	LoE	SoR	LoA
A	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.	n.a.	n.a.	9.7
B	Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.	n.a.	n.a.	9.8
C	Rheumatologists are the specialists who should primarily care for patients with RA.	n.a.	n.a.	9.9
D	Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life.	n.a.	n.a.	9.9
E	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.	n.a.	n.a.	9.4
	Recommendations			
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A	9.8
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.*	1a	A	9.7
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.	2b	B	9.3
4.	MTX should be part of the first treatment strategy.	1a	A	9.4
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A	9.0
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.	1a	A	8.9
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors*, other csDMARDs should be considered.	5	D	8.4
8.	If the treatment target is not achieved with the first csDMARD strategy, when and poor prognostic factors* are present, a bDMARD† or a tsDMARD‡ should be added.	1a	A	9.3
9.	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.	1a	A	8.9
10.	If a bDMARD# or tsDMARD## has failed, treatment with another bDMARD† or a tsDMARD‡ should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.	#1b ##5	A D	8.9

have a limited place, mainly reserved for patients with mild RA. As no new evidence regarding a good efficacy of hydroxychloroquine was found for RA in general and the historic studies had shown only weak clinical and no structural efficacy,[73] it was decided to keep the focus on sulfasalazine and leflunomide. In some countries, especially in Asia, also other agents like bucillamine or iguratimod have been approved for RA, but these drugs were not considered here given insufficient data in other regions. *LoE 1a, SoR A, LoA 9.0 (1.2).*

6. *Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible* (unchanged). There was much less discussion on the use of GC than ever before in the history of these recommendations, and there was unanimity that they should primarily be used as bridging therapy until csDMARDs exhibit their efficacy and that tapering GC rapidly (aiming at discontinuation within about 3 months) is important. Failure to sustain the treatment target on tapering or withdrawal of GC after the bridging phase should be regarded as failure of this therapeutic phase and thus elicit the institution of a bDMARD or a tsDMARD added to the csDMARD. Regarding the debate over whether treatment with bDMARDs or tsDMARDs should be preferred to csDMARDs plus GC, at least three trials have shown similar responses when MTX plus GC was compared with MTX plus bDMARDs[70 71 74] and no new data conflicting with this view have been published since then; tsDMARDs have not yet been compared with MTX plus GC. *LoE 1a, SoR A, LoA 8.9 (1.3).*[70 71 74]

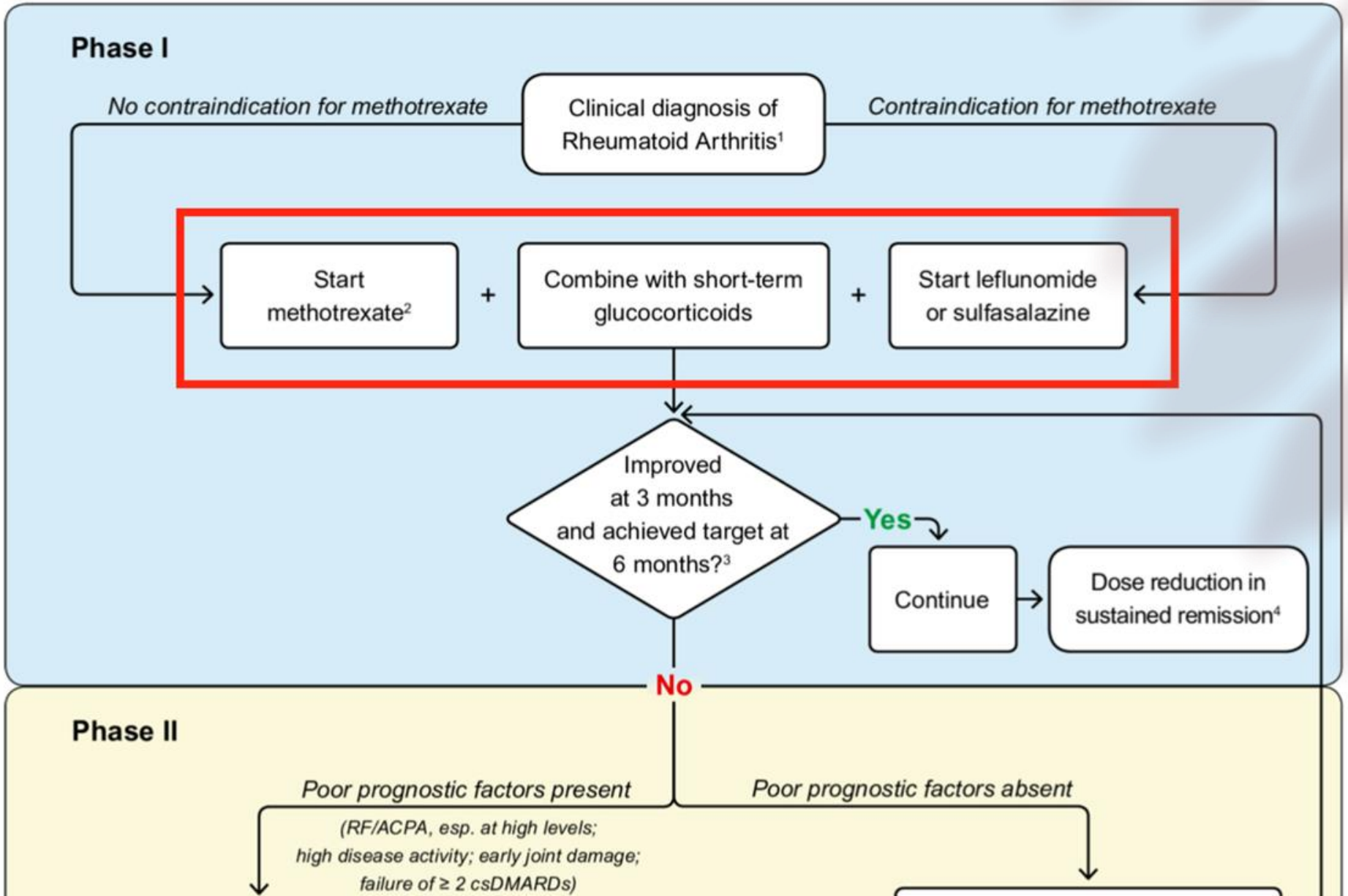
Regarding the first change, the task force also agreed that bDMARDs and tsDMARDs have on average similar efficacy and, therefore, no preference can be given to any of these agents for reasons of efficacy. While two studies designed as non-inferiority trials have shown statistical superiority of baricitinib or upadacitinib compared with adalimumab (all in combination with MTX),[80 81] a third study using tofacitinib+MTX did not show such superiority[82]; thus, the overall clinical relevance of small differences in clinical trials was not considered convincing enough for the task force to prefer tsDMARDs over bDMARDs. This conclusion is further supported by recently presented data revealing that filgotinib+MTX met non-inferiority for Disease Activity Score 28 <3.2, but not superiority criteria, when compared with adalimumab, a prespecified endpoint, although superiority was observed for some of the secondary endpoints.[83] Importantly, in these studies various inflammatory markers, such as swollen joint counts, did not differ among the groups, in line with the hitherto unknown clinical relevance mentioned above.

A third JAKi, peficitinib, has meanwhile been approved in Japan where clinical trials revealed significant efficacy[84 85]; in a global study, efficacy was not similarly apparent, possibly due to high placebo effects.[86]

A fourth JAKi, upadacitinib, has undergone testing in phase III trials in different RA populations as combination and monotherapy,[27] adding to the documented efficacy of this class of drugs; upadacitinib has meanwhile been approved at 15 mg daily by the FDA of the USA with a variety of warnings added to the prescribing information, including a warning that thromboses

70 Nam JL, Villeneuve E, Hensor EMA, *et al*. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the idea study). *Ann Rheum Dis* 2014;73:75–85.

71 Lund Hetland M, Haavardsholm EA, Rudin A, *et al*. A multicenter randomized study in early rheumatoid arthritis to compare active conventional therapy versus three biological treatments: 24 week efficacy and safety results of the NORD-STAR trial. *Arthritis Rheumatol* 2019;71:5237–40.



Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice

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ABSTRACT

Objective To develop recommendations on monitoring for adverse events (AEs) of low-dose glucocorticoid (GC) therapy (≤7.5 mg prednisone or equivalent daily) in clinical trials and daily practice.

Methods Literature was searched for articles containing information on incidence and monitoring of GC-related AEs using PubMed, EMBASE and Cochrane databases. Second, the authors searched for broad accepted guidelines on the monitoring of certain AEs (eg, WHO guidelines on screening for diabetes). Available data were summarised and discussed among experts (rheumatologists and patients) of the EULAR Task Force

Box 1 Recommendations

Three general recommendations on monitoring in clinical trials

1. Report all monitoring results of trials
2. Report both on the group level (eg, means) and on the individual patient level (eg, numbers)
3. Develop new tools for assessing specific adverse events

of high-dose GC therapy (>30 mg prednisone

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Table 1 Monitoring recommendations

Adverse event	Increased risk in RCTs N/A, data not available	Difficulties in interpreting results from RCTs c, conflicting data; s, small numbers; e, endpoint inaccurately defined	Increased risk in prospective cohort studies N/A, data not available	Status and relevance of AE c (LE), clinical endpoint (life expectancy); c (QoL), clinical endpoint (quality of life); s, surrogate endpoint; b, biomarker	Feasible method for monitoring purpose available	Monitoring advised –, not indicated; c, in clinical trials; d, in daily practice
Cardiovascular						
Dyslipidemia	No	e	–	s	Yes	c
Electrolyte disturbances	N/A	–	No	b	Yes	c
Edema	No	s e	–	c (QoL)	Yes	c d
Renal dysfunction (creatinine clearance)	N/A	–	N/A	b	Yes	–
Heart failure	No	s e	–	c (LE, QoL)	No	–
Hypertension	No	e	–	s	Yes	c d (standard care)
Ischemic CVD / atherosclerosis	No	s	–	c (LE, QoL)	No	c d (standard care)
Infectious						
Infections	Possibly	c e	–	c (LE, QoL)	No	c
Gastro-intestinal						
Peptic ulcer disease	Possibly	c s	–	c (LE, QoL)	Yes	c d (standard care)
Pancreatitis	N/A	–	N/A	c (LE)	Yes	–
Psychological						
Mood disturbances	Possibly	c s e	–	c (QoL)	No	c
Psychosis	N/A	–	Yes*	c (QoL)	No	c
Endocrine & metabolic						
Diabetes / glucose intolerance	Possibly	c e	–	s	Yes	c d
Body weight and fat redistribution	Possibly	c	–	c (QoL)	Yes	c d (standard care)
Interference with hormone secretion	Yes	s e	–	b	No	c
Dermatological						
Skin atrophy	N/A	–	N/A	c (QoL)	No	c
Acne, hirsutism, alopecia, bruisability	No	s e	–	c (QoL)	Yes	c
Musculo skeletal						
Osteoporosis (BMD)	Possibly	c e	–	s	Yes	c d
Osteonecrosis	N/A	–	Yes*	c (QoL)	No	c
Myopathy	N/A	–	Yes*	c (QoL)	No	c
Ophthalmological						
Cataract	No	s e	–	c (QoL)	Yes	c
Glaucoma (intra-ocular pressure)	Yes	s e	–	s	Yes	c d

*Data indicating that risk may be increased with high-dose glucocorticoid therapy.
The 'increased risk' columns describe the risk of occurrence for all adverse events (AEs). Preferably, data from randomised controlled trials (RCTs) were used. If lacking, data from

Recommendation

EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases

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ABSTRACT

To develop recommendations for the management of medium to high-dose (ie, >7.5 mg but ≤100 mg prednisone equivalent daily) systemic glucocorticoid (GC) therapy in rheumatic diseases.

A multidisciplinary EULAR task force was formed, including rheumatic patients. After discussing the results of a general initial search on risks of GC therapy, each participant contributed 10 propositions on key clinical topics concerning the safe use of medium to high-dose

the EULAR task force on GC therapy,[9] but these were mainly based on evidence and experience with low-dose GC therapy (ie, ≤7.5 mg prednisone equivalent daily). Proper advice on balancing advantages and disadvantages of medium/high-dose GC therapy is lacking. Therefore, this task force set out to develop recommendations for the use and management of systemic medium/high-dose GC therapy in rheumatic diseases.

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Table 2 The recommendations with strength of recommendation and level of evidence

	Proposition	SOR VAS; mean (95% CI)	SOR A+B %	SOR LoE
	Education and prevention			
1	Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium/high-dose GC treatment, and the potential risks associated with such therapy	91 (81 to 101)	100	III
2	Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care	75 (57 to 93)	75	III/IV
3	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions	91 (84 to 99)	100	I-A
4	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression	84 (67 to 101)	92	IV
5	Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners	80 (69 to 91)	75	IV
	Dosing/risk-benefit			
6	Before starting medium/high-dose GC treatment consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio	85 (76 to 94)	83	IV
7	Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment	85 (76 to 95)	92	I-A/IV
8	Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of AEs	82 (72 to 94)	92	IV
9	If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy	REJECTED		
	Monitoring			
10	All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs	85 (79 to 92)	75	IV

A+B %, percentage of the task force members that strongly to fully recommended this proposition based on an A—E ordinal scale (A, fully recommended, B, strongly recommended); AEs, adverse effects; CI, confidence interval; GC, glucocorticoid; LoE, level of evidence (table 1); SOR, strength of recommendation; VAS, visual analogue scale (0–100 mm 0= not

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

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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

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

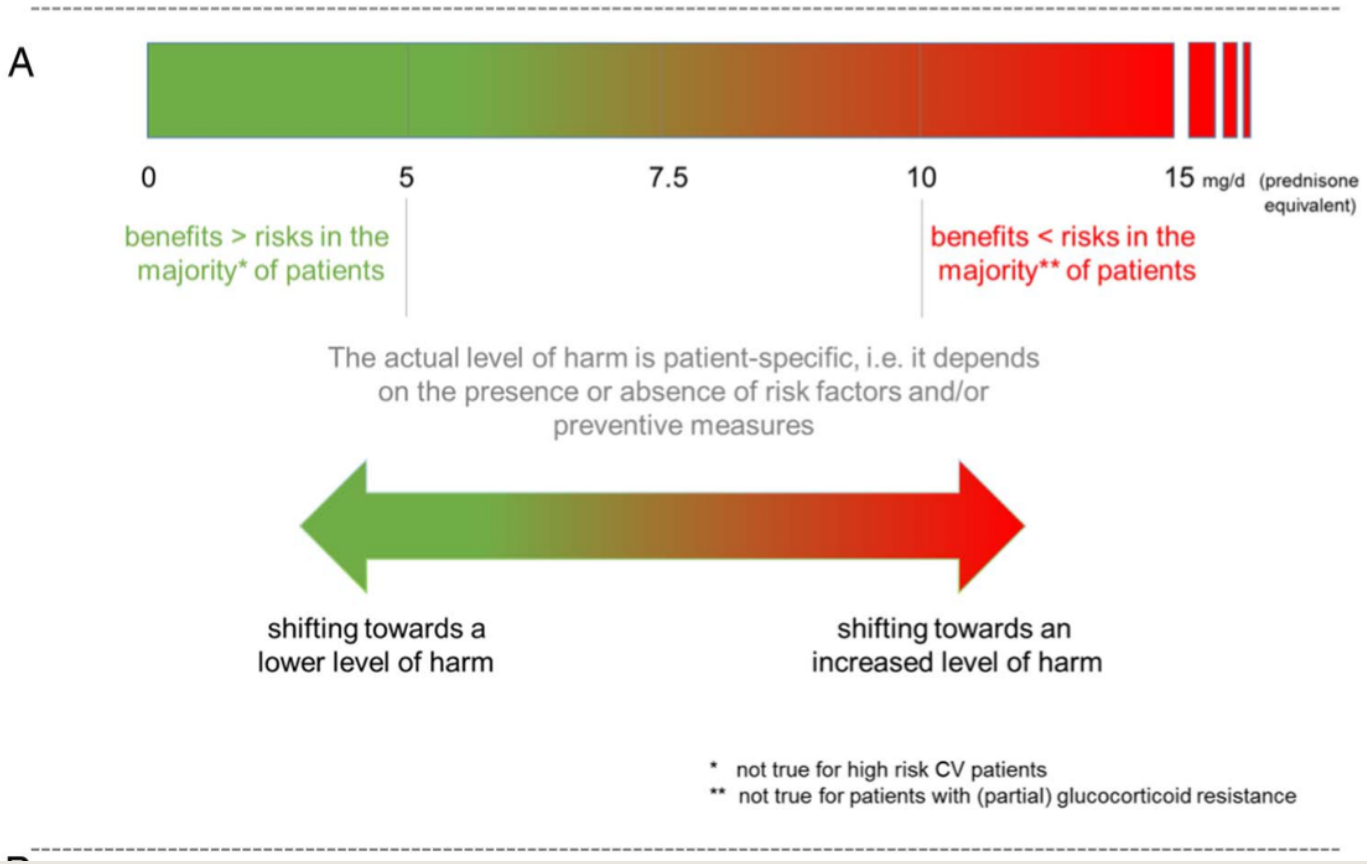

Figure 1 The level of harm of long-term glucocorticoid therapy in rheumatic diseases. Bearing in mind the beneficial effects of glucocorticoids, the Task Force members agreed that (A) at dosages of ≤5 mg/day prednisone equivalent, there is an acceptably low level of harm that is elevated at dosages of >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]

THANKS !!!