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# Low-dose glucocorticoids in rheumatic diseases: Introduction

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The Editor of *Clinical and Experimental Rheumatology*, Stefano Bombardieri, and the Co-Editors of this volume – Johannes W.J. Bijlsma, Jürgen Braun, Frank Buttgereit, Maurizio Cutolo, and Theodore Pincus – are pleased to present the 13th annual Supplement of *Clinical and Experimental Rheumatology* concerning Contemporary Topics in Rheumatic Diseases entitled “Low-dose Glucocorticoids in Rheumatic Diseases”.

This Supplement and previous annual supplements are directed to provide summaries of the latest scholarly research on an important contemporary topic for the rheumatology community, independent of commercial interests. The supplements are available on the Internet without charge at [www.clinexprheumatol.org](http://www.clinexprheumatol.org).

Previous supplements include:

Volume 17 (1999) – *Combination DMARD therapy in rheumatoid arthritis*

Volume 18 (2000) – *Bone mass in the rheumatic diseases*

Volume 19 (2001) – *Controversies in COX-2 inhibitor therapy*

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Volume 26 (2008) – *Mortality in Rheumatic Diseases*

Volume 27 (2009) – *A Systematic Comparison between Rheumatoid Arthritis and Ankylosing Spondylitis*

Volume 28 (2010) – *Methotrexate in Rheumatic Diseases*

The current Supplement concerning glucocorticoids in rheumatic diseases is designed to fill in important gaps in the literature, based on the following themes:

## 1) Glucocorticoids remain the most widely-used medication for inflammatory rheumatic diseases

In the international database of the Quantitative Clinical Assessment of Patients with Rheumatoid Arthritis (QUEST-RA) study, among 4,363 patients with rheumatoid arthritis (RA) seen in usual care at 48 clinical sites (~100 patients per site) in 15 countries, 66% of consecutive patients were taking glucocorticoids, including more than 70% in 6 countries (Argentina, Finland, France, Ireland, Serbia and USA), more than 50% in 7 other countries (Germany, Italy, Poland, Spain, Sweden, Turkey, and UK), and fewer than 50% only in Denmark (43%) and the Netherlands (26%) (1). In SLE, among 539 patients followed in the Johns Hopkins Lupus Cohort, 89% had been treated with glucocorticoids, and 57% of patients with a disease duration >10 years had always received these agents (2). Almost all patients with vasculitis, polymyositis, polymyalgia rheumatica, and most other inflammatory rheumatic diseases are treated with glucocorticoids.

The current widespread use of glucocorticoids in most patients with inflammatory rheumatic disease is presented in:

- **Glucocorticoid treatment in early rheumatoid arthritis**  
*D. Krause, R. Rau, J. Braun* p. S121
- **Glucocorticoids in systemic lupus erythematosus**  
*M. Mosca, C. Tani, L. Carli, S. Bombardieri* p. S126
- **Glucocorticoid treatment in spondyloarthritis**  
*C. Fendler, X. Baraliakos, J. Braun* p. S139

- **Glucocorticoid treatment of polymyalgia rheumatica**  
*R. Caporali, M.A. Cimmino, C. Montecucco, M. Cutolo* *p. S143*
- **Glucocorticoids in paediatric rheumatology**  
*A. Ravelli, B. Lattanzi, A. Consolaro, A. Martini* *p. S148*

**2) Introduction of glucocorticoids in 1948 was not preceded by current standards to introduce new medications to the market, such as randomised controlled clinical trials, documentation of adverse events, and description of dose-response relations for optimal efficacy, safety, and benefit/risk ratio:**

Glucocorticoids were administered initially to a patient with active RA in 1948 by Hench, who reported dramatic improvement within 2 days, documented by motion pictures, and published in 1949 (3). The 1950 Nobel Prize in Physiology and Medicine was awarded to Hench, Kendall and Reichstein for the discovery and clinical application of glucocorticoids. At that time, introduction of a new therapy did not require randomised controlled clinical trials – the first clinical trials were conducted only in the 1940s (4, 5). Information concerning adverse events, and dose-response relations to recognise optimal efficacy, safety, and benefit/risk ratio, particularly over long periods, also was not required. Clinical trials to document disease-modifying properties of prednisone were conducted only after glucocorticoids were available to all doctors and their patients (6, 7).

Imagine if a TNF-alpha inhibitor had been introduced as a new therapy in 1948, without clinical trials or studies of optimal dosage. It is possible that many clinicians might have prescribed substantially higher doses than those used initially, leading to frequent severe adverse events of infection. In such a scenario, there might have followed widespread recommendations against any use of TNF-alpha inhibitors, except possibly as “bridging therapy” or in dire circumstances.

The history of glucocorticoid use and insights into dose-response relations and routes of administration are presented in:

- **History of the development of corticosteroid therapy**  
*T.G. Benedek* *p. S5*
- **Glucocorticoids in rheumatology: indications and routes of administration**  
*J.W.G. Jacobs, J.W.J. Bijlsma* *p. S81*
- **Adverse events of intravenous glucocorticoid pulse therapy in inflammatory diseases: a meta-analysis**  
*N.A.M. Smits, N. Duru, J.W.J. Bijlsma, J.W.G. Jacobs* *p. S85*

**3) Low-dose glucocorticoids appear to have a substantially greater benefit/risk ratio than high-dose glucocorticoids.**

A reassessment of the teaching that glucocorticoids should be avoided in most RA patients began during the 1980s (8), along with recognition of severe long-term outcomes of RA (9, 10). The efficacy and safety of low doses of glucocorti-

coids were documented in an open study reported in 1964 (11), a 24-week non-blinded clinical trial reported in 1982 (8), and six more recent clinical trials (see below).

The greater benefit/risk ratio of low-dose glucocorticoids compared to high-dose glucocorticoids, including disease-modifying properties of low-dose glucocorticoids, is presented in:

- **The COBRA trial 20 years later**  
*M. Boers* *p. S46*
- **The origins, results and consequences of the 1995 Arthritis Research Campaign low-dose glucocorticoid study**  
*J. Kirwan* *p. S52*
- **Glucocorticoids in rheumatoid arthritis: lessons from the Utrecht study**  
*J.W.G. Jacobs, J.W.J. Bijlsma* *p. S59*
- **Effects on joint destruction and remission, bone turnover and lack of influence on atherogenesis: a review of the BARFOT low-dose prednisolone studies on patients with early RA**  
*B. Svensson, I. Hafström* *p. S63*
- **A dose of only 5 mg prednisolone daily retards radiographic progression in early rheumatoid arthritis – The Low-Dose Prednisolone Trial**  
*S. Wassenberg, R. Rau, H. Zeidler* *p. S68*
- **The clinical efficacy of 3 mg/day prednisone in patients with rheumatoid arthritis: evidence from a randomised, double-blind, placebo-controlled withdrawal clinical trial**  
*T. Pincus* *p. S73*
- **Safety of glucocorticoids – clinical trials**  
*J.A.P. da Silva* *p. S99*

**4) New information concerning mechanisms of action and chronobiology of glucocorticoids suggests potential new therapeutic approaches.**

New information concerning glucocorticoid pharmacodynamics, the effects of alterations of the hypothalamic-pituitary-adrenal (HPA) axis on inflammatory diseases, the glucocorticoid receptor, and regulation of glucocorticoids by the central nervous system has provided new understanding of mechanisms of action and approaches to better therapies. These topics are presented in:

- **Pharmacodynamics of glucocorticoids**  
*C. Strehl, C.M. Spies, F. Buttgerit* *p. S13*
- **Regulation of glucocorticoids by the central nervous system**  
*M. Cutolo, F. Buttgerit, R.H. Straub* *p. S19*
- **Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases – a role for misguided energy regulation**  
*R.H. Straub, F. Buttgerit, M. Cutolo* *p. S23*
- **Glucocorticoid receptor: implications for rheumatic diseases**  
*T. Kino, E. Charmandari, G.P. Chrousos* *p. S32*

- **Prednisone chronotherapy**  
C.M. Spies, M. Cutolo, R.H. Straub,  
G.-R. Burmester, F. Buttgerit p. S42
  
- 5) Knowledge of benefit/risk ratio of low-dose glucocorticoids over long periods requires both clinical trials and long-term observational studies.**  
Randomised controlled clinical trials are the optimal method to analyse efficacy and adverse effects of any medication compared to a placebo or other control treatment. However, clinical trials have many limitations, particularly in chronic diseases – including a short time frame, inflexible dosage schedules, and patient selection – which inevitably limit application of results in actual clinical care, particularly over long periods. It is difficult or impossible to study adverse effects of glucocorticoids adequately over fewer than 5 years. Therefore, clinical trials require supplementation with observational data, as addressed in:
  
- **Rheumatoid arthritis and glucocorticoids; the contribution of a literature search to the development of a EULAR recommendation on treatment with glucocorticoids in RA**  
S.L. Gorter p. S77
  
- **Glucocorticoid-induced osteoporosis**  
D. den Uyl, I.E.M. Bultink, W.F. Lems p. S93
  
- **The safety of low-dose glucocorticoids in rheumatic diseases**  
Y.G. Hwang, K. Saag p. S104
  
- **Low-dose glucocorticoids and disease-modifying drugs in patients with rheumatoid arthritis**  
O. Malysheva, C.G. Baerwald p. S113
  
- **Toward safer treatment with glucocorticoids: via patient and rheumatologist perspectives to recommendations on monitoring for adverse events**  
M.C. van der Goes, J.W.G. Jacobs,  
J.W.J. Bijlsma p. S116
  
- **Long-term prednisone in doses of less than 5 mg/day for treatment of rheumatoid arthritis (RA): personal experience over 25 years**  
T. Pincus, I. Castrejón, T. Sokka p. S130

The Editor and Co-Editors hope that you find the Supplement interesting and informative, and that it will lead to better patient care and improved long-term outcomes for people with rheumatic diseases.

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