



Report of the
 FIFTH JOINT WHO/ILAR TASK FORCE MEETING
 ON RHEUMATIC DISEASES
 29 June - 2 July 1993, Geneva

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Les opinions exprimées dans les documents par des auteurs cités nommément n'engagent que lesdits auteurs.

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1. INTRODUCTION

The meeting was opened by Dr N.G. Khaltaev on behalf of the Director-General. Dr Khaltaev welcomed the members of the Task Force to Geneva. Dr Khaltaev summarized the prepared remarks which noted that the rheumatic diseases were important to world health because they limit work performance and social integration. Osteoporosis has become the focus of public awareness as an important disease in public health, particularly because of high fracture rates and subsequent morbidity and mortality.

Dr K.D. Muirden, President of ILAR, was elected Chair, Dr J.P. Edmonds, Secretary General of ILAR, was elected Vice-Chair, and both Dr P.M. Brooks and Dr C.H. Goldsmith were elected Rapporteurs.

Dr Muirden extended thanks to Dr N.G. Khaltaev and his staff for their hard work in helping to coordinate the meeting. Dr A.S. Russell, Treasurer of ILAR, was most helpful in coordinating the relationships with the pharmaceutical industry.

This meeting, the fifth WHO/ILAR task force, extended the work of a fourth meeting chaired by Dr K.D. Muirden held in Geneva, and the third meeting chaired by Dr. L. Shulman, also held in Geneva, which surveyed the status of rheumatic diseases, their pathogenesis and treatment in general. The fourth meeting focused on certain aspects of antirheumatic therapy and developed guidelines for the use and evaluation of antirheumatic therapies in Rheumatoid Arthritis, Osteoarthritis and Gout. From that meeting a proposed new classification of antirheumatic drugs has been developed, dividing them into symptom modifying or disease controlling antirheumatic therapies: (See Table)

TABLE: Proposed classification of antirheumatic therapies

1.	Symptom modifying antirheumatic drugs (SMARD) These improve the symptoms and clinical features of inflammatory synovitis.
	I. Nonsteroidal antiinflammatory drugs (NSAID)
	II. Corticosteroids
	III. Slower acting drugs, e.g., antimalarials, gold, D-penicillamine, antimetabolites, cytotoxic agents (Category III SMARD)
2.	Disease controlling antirheumatic therapy (DC-ART) These change the course of RA, i.e., they both
	(a) improve and sustain function in association with inflammatory synovitis, and
	(b) prevent or significantly decrease the rate of progression of structural joint damage.
	These changes must be sustained for a minimum period of 1 year; the classification must include reference to the time period for which criteria have been satisfied, e.g., 2 year DC-ART.

The current meeting focused on disease controlling anti-rheumatic therapies, their definition, measurement, and future data collection to derive world standards for therapy assessment. Protocols for slow acting drugs in osteoarthritis patients were also discussed. Guidelines for drug use initiated in the fourth task force, circulated to the Regional Leagues and edited in reaction to discussion, were approved for implementation. Symptom Modifying Drug (NSAID) testing protocols were approved and core outcomes for symptom modifying endpoints in clinical trials were also approved.

2. DISEASE CONTROLLING ANTIRHEUMATIC THERAPY(DC-ART)

This new classification was thought to be more logical and to set treatment objectives for arthritis. It was felt that it also might produce research and development of new agents even though its components were yet to be clearly defined. Some concern was expressed that the new classification might be abused leading to development of drugs purely to fit the classification and it was felt that the new classification should not be used for these purposes until it had been validated.

The principal effects of anti-rheumatic drugs should be to:

- i) improve and sustain function,
- ii) decrease inflammatory synovitis,
- iii) prevent structural damage.

A review of clinical trials of anti-rheumatic drugs summarized the importance of entry criteria, i.e., choosing those patients with progressive and responsive disease and the appropriateness and type of control group. Blinding of observers was felt to be important for the first year of a trial but not so important after that. Analysis of data must be intention-to-treat and all patients should be followed for the duration of the trial (including dropouts). Trials of anti-rheumatic drugs in the future should if possible involve patients with early RA referred by primary care physicians.

2.1 Improve and Sustain Function

There was a clear consensus that function included physical, emotional and social dimensions and that these measures of function (at least for physical) correlated with mortality in patients with RA. Currently used measures do not address the important issues of toxicity and economics. Measurements of utility should be adopted to include these variables in future trials. Comorbidity was particularly important in RA patients and needed to be included in measures of outcome. Any measure of improvement needs to be clinically relevant and should be sustained over time.

2.2 Decrease Inflammatory Synovitis

The assessment of inflammatory synovitis is an essential component in the evaluation of the new classification of anti-rheumatic drugs. Synovial inflammation can be measured indirectly by evaluation of:

- a) indirect consequences such as joint tenderness, pain and stiffness, decreased grip strength (for upper extremities) and walking time (for lower extremities), overall global measures of disease activity, or laboratory measures of inflammation (acute phase reactants, cytokine or other mediator levels) and indirect measures of synovial mass (cytamine deaminase);
- b) measurement of synovial thickening by observation, palpation or imaging techniques;
- c) direct assessment of synovial inflammation by synovial biopsy.

It was felt that of the indices of instruments that aggregate several measures into one single index, the Scott, DAS and Paulus indices offered the best available, but that much more work should be done on the new imaging techniques for measuring synovial thickening such as MRI and ultrasound. It was also noted that these were expensive and needed to be validated, and would probably not be widely available, particularly in developing countries.

Synovial biopsy was a relatively simple technique and should be pursued by certain groups in terms of standardization of procedure, sampling and assessment of inflammation. It would also need to be

validated in respect to other new direct measures of synovial inflammation.

The meeting recommended that:

Decreased inflammatory synovitis be defined according to modified DAS criteria and modified Paulus criteria - slightly different for SM-ARD and DC-ART's so many of these recommendations are provisional and based on reasonable and arbitrary criteria, which will need to be tested in a prospective series of patients.

Both a mean response (DAS) and per patient response (Paulus) will be considered.

Criteria will be derived directly from the WHO/ILAR Core Endpoints (see below) for both DAS and Paulus measures; (1) Swollen Joint Count and (2) Tender Joint Count are provisionally based on the reduced, 28 joint count (for study purposes does not include MTPs or toes - although these are clearly not to be ignored in clinical practice).

2.3 Prevent or Significantly Decrease Rate of Progression of Structural Joint Damage

Although it was felt useful to develop a clinical measure of damaged joints such as the Joint Assessment and Mobility Scale (Paulus, 1992) it was decided that radiological change would remain the most important measure of damaged joints.

At present plain X-rays of the hands and wrists would be the standard with loss of joint space and erosions being the variables amenable to scoring. Scoring methods should be reproducible and amenable to change.

Different radiological criteria might have to be developed for the different stages of the disease:

- < 1 yr (non erosive) - prevention of erosions
- 1 - 5 yr - prevention of new erosions
- > 5 yr - prevention of joint destruction

Juxta-articular erosions and joint space narrowing may need to be reviewed separately or combined and studies should be conducted over sufficient time to assess change.

Further development should be done to obtain precise definitions of erosions and other aspects of joint damage and to specify methodology (which joints, which view, scoring (blind or not), type of film, same radiographer, etc.).

Further information is required on the number of patients developing erosions, new erosions or joint damage each year to be able to define success of therapy. It should be appreciated that cartilage and bone destruction do not proceed in a linear fashion and that it is much more rapid in the early years of RA. While X-rays assess bone damage other measures (imaging or biochemical) are required to evaluate cartilage destruction.

2.4 Are there Special Considerations Relevant to Trials of Biological Agents?

Biological therapies may vary from other drugs in several respects:

- they tend to have a more specific mechanism of action,
- they have long lasting effects on disease activity.

Biologicals are likely to be used with other drugs which may blunt or enhance responses and this may raise practical design issues in early trials. Biologicals may be used for different aspects of the disease (i.e., as induction or maintenance therapy) and it will be important to assess these different aspects of disease control. Short and long term side effects will need to be assessed in view of the immunogenic potential of these agents. Development of these agents requires:

1. Standardization of protocols (including endpoint measures),
2. Development of criteria for remission and flare of disease,
3. Close collaboration with industry and regulatory authorities,
4. Rapid exchange of information regarding these agents.

3. SPECIAL CONSIDERATIONS OF DC-ARTS

3.1 Patient Stratification

Stratification of patients is essential to reduce confounding effects and to overcome inequalities in response characteristics between groups. There is some evidence to suggest that the chance of improvement in RA patients is much more likely with disease duration < 5 yr than with ≥ 5 yr. Post hoc stratification may be a useful means of hypothesis generation when reviewing therapy responders and non-responders.

3.2 Changing Technologies

New methods of plain X-ray assessment have not proved beneficial and it is considered better to standardize current plain radiographs. MRI may provide an extremely valuable measure of cartilage volume, but requires further development and evaluation. Development of molecular techniques for cytokine gene expression and production may add valuable information to synovial tissue analysis in assessment of response to antirheumatic drugs.

3.3 Proportion of Response which Constitutes a Positive Response

While there are validated indices of RA disease activity, there is considerable variability in rheumatologists evaluation of response on an individual patient. At present improvement in several measures needs to be observed. In view of the WHO/ILAR core endpoints. It was proposed that the following core measures be used:

- (1) Swollen Joint Count
- (2) Tender Joint Count
- (3) Assessor or Patient global (Assessor global not presently in DAS)
- (4) Pain VAS (not presently in DAS)
- (5) Acute Phase Reactant (ESR, CRP)
- (6) Functional measure to be the 6th for SM-ARDs
- (7) X-ray (in studies ≥ 1 year)
- * SM-ARD will require ≥ 5 of first 6 measures
- * DCART - Functional plus ≥ 4 of first 5 measures

The number of joints to be counted will provisionally be based on the 28 joint count (useful for study purposes does not include MTP and toes - although these joints are clearly important in clinical practice they add little information to Tender Joint Count in trials of SM-ARDs).

Preliminary criteria for trials will:

- a) require minimal active disease (defined as minimum disease activity criteria will require > 15 Swollen Joints* plus $>$ placebo $+2$ SD for baseline Patient and Assessor globals and ESR > 28 mm/hr. [* if 28 Joint Count is adopted this criterion will be adjusted from the present 68 after examining for linear relationship between 28 and 68 Swollen Joint Count.]
- b) accept $> 20\%$ improvement in Swollen Joint Count, Tender Joint Count, Pain and ESR plus $> 40\%$ change in Assessor or Patient global [All carry-over from the recommendations of Paulus et al.]

Further study is required to:

- i. Define accurate number or % change needed for definition of mean placebo response at 2 SD for each of the above criteria (assume pain and global placebo responses by using previous studies. These will be substituted for the $> 20\%$ criteria. These criteria will define very stringent criteria of response, although they will be reviewed for "common sense" as well.
- ii. Examine the relationship between the reduced 28 Swollen Joint Count - without assuming a clear relationship, to assess the reduction in Swollen Joints for minimum activity criteria (relative to the present 15 of 68 Swollen Joints).
- iii. Examine the effect of separately evaluating Swollen Joint Count and 3 of 4 criteria to see if this approach (which emphasizes Swollen Joints in the measurement of "decreased inflammatory synovitis") is different from the 4 of 5 criteria mentioned above.
- iv. That investigations be encouraged to examine the relationship between Synovial Biopsy, histology, cell markers, cytokines and clinical responses in prospective studies to corroborate or supplement the above definitions of disease activity and response.

3.4 Observational Studies vs Experiments

Clinically based observational studies provide important data on long term morbidity in

patients with RA. RCT's, including placebo, although expensive and often short term are still the gold standard for assessment of interventions in patients with arthritis.

4. TESTING PROTOCOLS FOR SLOW ACTING DRUGS FOR OSTEOARTHRITIS (OA)

Slow acting drugs for patients with OA can be classified as symptomatic slow acting drugs (SYSADOA) or chondroprotective drugs. These two types of agents should be clearly defined and trials to demonstrate efficacy appropriately designed.

OA is a heterogeneous disease and diagnostic criteria have to be joint specific. The issue of concomitant therapy (analgesic or NSAID), endpoint measures and in particular an appreciation of the biopsychosocial disease model in the context of endpoints needs to be considered.

Both short acting and long acting drugs that treat symptoms or disease processes in OA could be evaluated using the same outcomes measures. Some drugs act quickly and others take a longer time to control symptoms and, although the short acting drugs ultimately affect the same outcomes, symptoms in OA, there may be some value in describing some therapeutic agents as slow acting and others as shorter acting.

Preliminary criteria for clinical trials for symptomatic and chondroprotective drugs were proposed.

4.1 Symptomatic Slow Acting Drugs for OA

Definition: Symptom modifying therapy in OA is that which reduces specified symptoms of OA in humans.

Trials of symptom modifying therapy should be conducted in accordance with the WHO/ILAR recommendations.

Symptom reduction in an individual patient will be indicated by specified amount of reduction in specified symptoms.

Symptom reducing therapy will be indicated by symptom reduction in a specified proportion of patients.

There is an urgent need to establish these criteria and a range of measures and techniques which are candidates for these endpoint measures. Evaluation of these candidate measures is a priority but current opinion is that appropriate candidate measures are:

- i. The WOMAC Index,
- ii. The Lequesne Index,
- iii. Their component parts (ie, various measures of pain, stiffness and physical disability).

Data should be collected from therapeutic and other clinical studies in OA to subject the various candidate measures to validity testing, and should include at least one of the candidate measures in each study.

Psychosocial adaptation may influence some of these endpoint measures. This area requires review with the intention of identifying appropriate psychosocial assessments.

4.2 Chondroprotective Agents

Definition: Chondroprotective therapy in OA is that which prevents, retards or reverses the articular cartilage lesions in humans.

Trials of chondroprotective therapy should be: randomized, placebo-controlled, conducted in well-characterised, specific, homogenous patient groups, and conducted over sufficient time. Current opinion is that this may take two or more years.

Endpoint measures for these trials are provisionally recommended as:

1. At the hip; progressive changes in joint space narrowing (inter bone distance) on plain X-rays.
2. At the knee; progressive changes in joint space narrowing (inter bone distance) in the medial tibia-femoral compartment on plain A-P standing (weight bearing) films.
3. At other joint sites; this remains undefined.

Progressive joint space narrowing in an individual patient will be indicated by a specified amount of reduction of joint space narrowing which will be defined as 2 SD (or equivalent) of the cross-sectional

method of measurement.

4.3 Intra-articular Drugs

A number of intra articular therapies had been evaluated for arthritis. These may be SYSADOADs or DMOADs but would have prespecified issues in clinical trial methodology. These would include issues such as concomitant therapies (discontinuation or not of NSAIDs) use of placebo injection, technique of injection and aspiration of joint fluid. Outcome measures that require further development include function, pain and inflammation.

5. GUIDELINES FOR ANTIRHEUMATIC DRUG USE

The guidelines for the following anti-rheumatic agents were ratified:

- Analgesics
- NSAIDs
- Slow Acting Anti-Rheumatic Drugs
- Corticosteroids
- Hypouricaemic Drugs

(See ANNEX V)

6. PROTOCOL FOR TESTING SM-ARDS(NSAIDS)

The protocol for the clinical testing of SM-ARDS (NSAIDs) were discussed and ratified.

(See ANNEX VI)

7. WHO/ILAR CORE ENDPOINTS FOR SM-ARDS IN RHEUMATOID ARTHRITIS (RA) CLINICAL TRIALS

The history of the development of endpoint criteria for clinical trials for patients with RA was reviewed. This included the history of the ACR Committee on RA measures, the EULAR Committee on endpoint measures and the OMERACT Conference. After subsequent discussion about possible grouping of the criteria, and the need for studies of validity and possible indices for combining these criteria, the meeting adopted the following 8 criteria as the WHO/ILAR core endpoints for SM-ARDS in RA trials:

- Swollen Joint Count
- Pain
- Tender Joint Count
- Assessor Global
- Patient Global
- Acute Phase Reactant
- Physical Function
- X-ray (in studies \geq 1 year)

Plans for further research were agreed to at the meeting:

1. Development and implementation of validation protocols for the testing of different methods to assess the OMERACT endpoints.
2. Establish the magnitudes of clinical importance for each of the endpoints and indices.

3. Develop indices of the OMERACT endpoints.
4. Develop measures of toxicity, emotional function, social function, patient preference and utility.
5. Develop life time percentiles for function and structural progression.
6. Develop methods for economic evaluation.

8. RECOMMENDATIONS

1. That the new classification of Anti Rheumatic Drugs be approved.
2. That the core set of endpoint measures approved by the meeting be promulgated by ILAR and the Regional Leagues for use in all trials of Anti Rheumatic Drugs and the use of additional endpoints be encouraged.
3. That functional measures be defined and developed to include psychosocial and emotional issues.
4. That techniques to measure synovial inflammation be developed.
5. That ILAR encourage validation of synovial biopsy as a measure of inflammation for use in therapeutic trials.
6. That WHO/ILAR promote close collaboration between clinicians, the pharmaceutical industry and regulatory agencies for the development, testing and dissemination of knowledge on biological agents.
7. That development of validated response criteria for DC-ARTs be developed.
8. That preliminary proposals for the testing of SYSADOADs and DMOADs be adopted.
9. That guidelines for use of: Analgesics, SM-ARDs (NSAIDs), SM-ARDs (SAARDs), SM-ARDs(Corticosteroids), Hypouricaemic Drugs be adopted and promulgated through the Regional Leagues.
10. That the protocol for testing SM-ARDs (NSAIDs) be promulgated through the Regional Leagues.
11. That international multi-center trials of ARD be encouraged within and between the Regional Leagues through the ILAR Committee on Clinical Trials.
12. That ILAR establish close links between the Clinical Trials, Epidemiology and Education Committees to coordinate ongoing development, testing and dissemination of therapeutic issues and antirheumatic drugs.

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* Unable to attend

ANNEX II: LIST OF WORKING PAPERS

DBO/TFRD/93/WP.1	Draft Agenda
DBO/TFRD/93/WP.2	List of Participants
DBO/TFRD/93/WP.3	Programme of Work
DBO/TFRD/93/WP.4	The DC-ART (Disease Control Anti-Rheumatic Therapy). Concepts and Future Directions Professor J.P. Edmonds
DBO/TFRD/93/WP.5	DC-ART Classification. Relevant Clinical Trials Drs H.E. Paulus and K.J. Bulpit
DBO/TFRD/93/WP.6	Disease Controlling Anti-Rheumatic Treatment. Dr J. Darmawan
DBO/TFRD/93/WP.7	Improvement and Sustained Improvement in Function. Dr P. Tugwell and P. Baker
DBO/TFRD/93/WP.8	Decreased Inflammatory Synovitis. Dr D. Furst
DBO/TFRD/93/WP.9	Decreased Inflammatory Synovitis. Professor A.N. Malaviya
DBO/TFRD/93/WP.10	Disease Controlling Antirheumatic Therapy: Preventing or Significantly Decreasing The Rate of Progression of Structural Joint Damage. Dr D.L. Scott
DBO/TFRD/93/WP.11	Disease Controlling Anti-Rheumatic Therapy - Commentary. Professor S. El-Badawi
DBO/TFRD/93/WP.12	Are There Any Special Considerations Relevant to Trials of Biological Agents? Dr V. Strand
DBO/TFRD/93/WP.13	The Need for Patient Stratification in DC-ART Evaluation. Professor J.P. Edmonds
DBO/TFRD/93/WP.14	DC-ART: The Relevance of Patient Stratification Dr Bosi Ferraz
DBO/TFRD/93/WP.15	Potential Application of Newer Technologies Professor A.S. Russell and Dr W.P. Maksymovych
DBO/TFRD/93/WP.16	Disease Controlling Anti-Rheumatic Drugs: What Proportion of Response Constitutes a Positive Response? Drs P.L.C.M. van Riel and L.B.A. van der Putte
DBO/TFRD/93/WP.17	Can Observational Studies Replace or Complement Experiment? Dr S. van der Linden
DBO/TFRD/93/WP.18	Guidelines for Testing Slow Acting Drugs in Osteoarthritis (SADOA). Drs M. Lequesne, R. Altman, N. Bellamy, K. Brandt, J. Menkes, R. Moskowitz, J.P. Pelletier
DBO/TFRD/93/WP.19	Intra-Articular Treatment of Osteoarthritis. Professor C. Menkes
DBO/TFRD/93/WP.20	Final Guidelines for The Use of NSAIDS Dr J. Darmawan
DBO/TFRD/93/WP.21	Guidelines for The Use of Slower Acting Agents. Dr D.L. Scott
DBO/TFRD/93/WP.22	Guidelines for Corticosteroids. Professor P.M. Brooks
DBO/TFRD/93/WP.23	Guidelines for The Use of Anti Hyperuricaemic Agents in Rheumatic Diseases. Dr O. Hubscher
DBO/TFRD/93/WP.24	Analgesics - Discussion Paper - Professor A.S. Russell
DBO/TFRD/93/WP.25	Protocol For Evaluation of NSAIDS. Professor P.M. Brooks
DBO/TFRD/93/WP.26	WHO/ILAR Core Endpoints For Symptom Modifying Antirheumatic Drugs in Rheumatoid Arthritis Clinical Trials. Drs M. Boers, P. Tugwell, D. Felson, P.L.C. van Riel, J.R. Kirwan, J.P. Edmonds, J. Smolen, N.G. Khaltsev, and K.D. Muirden
WHO/DBO/TFRD/91.1	Report of the Fourth Joint WHO/ILAR Task Force Meeting on Rheumatic Diseases.

Khaltsev NG: Opening Remarks. Fifth Joint WHO/ILAR Task Force Meeting on Rheumatic Diseases.

Nassonova V: Comments to: Can Observational Studies Replace of Complement Experiment? by van der Linden.

Woodcock J: Commentary on: Are There Special Considerations Relevant to Trials of Biologic Agents? by Strand.

Woodcock J: Commentary on: Can Observational Studies Replace of Complement Experiment? by van der Linden.

Goldsmith CH: Commentary on: Can Observational Studies Replace of Complement Experiment? by van der Linden.

Katz LM: Comments to: The DC-ART (Disease Controlling Anti-Rheumatic Therapy) Concept and Future Directions.

Smolen JS: Comments on: The DC-ART (Disease Controlling Anti-Rheumatic Therapy) Concept and Future Directions.

Darmawan J: Comments on: Disease Controlling Anti-Rheumatic Therapy Review of Relevant Clinical Studies by Paulus & Bulpit.

Chahade WH: Comments on: Disease Controlling Anti-Rheumatic Therapy Review of Relevant Clinical Studies by Paulus & Bulpit.

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ANNEX IV: GLOSSARY OF TERMS

ACE	Angiotension-1 converting enzyme
ARD	Anti Rheumatic Drug
CRP	C-reactive protein
DAS	Disease Activity Score
DC-ART	Disease Controlling Anti Rheumatic Drug
DMOAD	Disease Modifying Osteoarthritis Drug
EC	European Community
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration, USA
Health Care Worker	A person who delivers health care to patients but may not be medically qualified; nurse, village health worker, etc.
IA	Intraarticular
ILAR	International League of Associations for Rheumatology
IM	Intramuscular
IV	Intravenous
Medical Practitioner	A physician, medical doctor, or similarly qualified individual licence to prescribe drugs in a country.
MRI	Magnetic Resonance Imaging
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	Over the counter, non-prescription distribution of drugs
RA	Rheumatoid Arthritis
Rheumatologist	A medically qualified physician with specialty training in the rheumatic diseases and their treatment.
SAARD	Slow acting antirheumatic drug
SLE	Systemic Lupus Erthymatosus
SM-ARD	Symptom Modifying Anti-Rheumatic Drug
SYSADOAD	Symptomatic Slow Acting Disease Osteoarthritis Drug
USA	United States of America
WHO	World Health Organization

ANNEX V: REVISED GUIDELINES FOR ANTIRHEUMATIC DRUG USE

The indications for use of these agents in the Rheumatic Diseases follows these general criteria.

A. Indications for use
Relative/Absolute
Contraindications

B. Usage
Dose - Starting
 - Continuing
 - Specific Situations: Pregnancy, Elderly, Lactation
 - Social and Cultural Variations

Administration

Route: Oral, Suppository, IM, IV

Formulation

Interactions

Other Drugs

Food

Measures of Efficacy

C. Toxicity
Major Adverse Reactions
Monitoring for toxicity

D. Reasons for stopping therapy

E. Advice to patients.

V.1 Analgesics

A. Indications for Use

Analgesics should be used to relieve pain, one of the main objectives in the treatment of the rheumatic diseases. Health care workers should be aware that many of their patients will self-medicate for pain and that not all medications prescribed for pain are directly analgesic.

B. Usage

Analgesia is achieved by narcotics, non-opiate analgesics including aspirin (acetyl salicylic acid), acetaminophen (paracetamol), small doses of NSAIDs, traditional and herbal medicines, transcutaneous nerve stimulation, massage, manipulation, ultrasound, heat, cold, and psychotropic drugs. These drugs are commonly taken orally, however, suppositories, osteoarthritis patches and injections are also used. It should be remembered that even though an NSAID may be marketed for its analgesic properties, it is likely to possess the same side effects profile as other NSAIDs.

C. Toxicity

Analgesic drugs can cause anaphylactoid attacks, liver problems, and gastrointestinal bleeding - analgesic nephropathy can be associated with compound analgesic usage over long periods of time. Tinnitus is often a side effect of the high doses used to treat some rheumatic diseases.

D. Therapy Cessation

Analgesics should be ceased if major adverse reactions occur. Narcotics should be withdrawn slowly after chronic use. Patients, particularly those who self medicate, should be encouraged to seek the help of health care workers if these side effects occur.

E. Patient Advice

Patients with rheumatic diseases should be counselled as to the common side effects of analgesic therapy and counselled regarding non-drug forms of pain relief. Some side effects such as tinnitus can be handled by dose reduction, however, serious side effects such as blood in the stool, blackened stools, gastrointestinal pain and anaphylactoid reactions should be brought to the immediate attention of a health care worker.

V.2 Non-Steroidal Anti-Inflammatory Drugs

A. Indications for Use

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be used for the treatment of generalized inflammatory rheumatic diseases: ie, Rheumatoid Arthritis, Gout, Seronegative Arthritis, or Systemic Connective Tissue Diseases. They should not be used as initial therapy for degenerative diseases or soft tissue rheumatic diseases. It was felt in general that there was overuse of oral NSAIDs and that more emphasis should be made of non pharmacological therapies in Osteoarthritis and soft tissue rheumatism. With increasing use of NSAIDs given transdermally, there is a need for appropriate evaluation of this route.

B. Usage

Individual variability in response to these agents should be appreciated. The recommended daily doses are seen in the accompanying paper. Once symptomatic relief has been achieved the dose should be reduced and in some situations can be ceased. Prescribing of NSAIDs in pregnancy and lactation should be reduced to a minimum. NSAIDs are best taken with food to reduce gastric intolerance. NSAIDs may interfere with the hypotensive effects of beta blockers, ACE inhibitors and vasodilators as well as the diuretic effects of thiazides and other 'loop' diuretics. It is appropriate to continue if this interaction occurs with NSAIDs or antihypertensive medication.

The major measures of efficacy are: reduction in pain, stiffness and joint swelling, and if these do not respond within 7-14 days (depending on drug half-life), at appropriate dosage, then the NSAID should be changed. Allergic reactions may also occur particularly in those persons with a history of allergic rhinitis and asthma.

C. Toxicity

NSAIDs should be used with great care in the elderly or those with a history of renal and liver impairment. The issue of ulcer prophylaxis may be considered in those patients requiring NSAIDs who fulfil the following criteria: age > 65 years, female, previous peptic ulcer, significant disability or concomitant

steroid treatment. All patients commencing an NSAID should be questioned on whether they have had a previous osteoarthritis or melena. Further work needs to be done in this area to identify those at risk from significant gastrointestinal toxicity with NSAIDs and the exact role of ulcer prophylaxis. Allergic reactions may also occur particularly in those persons with a history of allergic rhinitis and asthma.

D. Therapy Cessation

NSAIDs should be ceased if major adverse reactions occur, if the disease for which the NSAID is being prescribed goes into remission or if the NSAID does not seem to be providing relief of symptoms.

E. Patient Advice

Patients should cease NSAIDs and report to their health care advisor if gastrointestinal or other serious untoward events occur when taking NSAIDs. NSAIDs should not be taken with alcohol, coffee, jalapena and nicotine until safety of these combinations has been established.

V.3 Slower Acting Drugs (SAD)

A. Indications for Use

Chronic inflammatory rheumatic diseases such as Rheumatoid Arthritis or seronegative arthritis. Treatment should be initiated only by a medical practitioner with special training in the use of these agents. Slower Acting Drugs will be either symptom modifying (SM-ARDs) or disease controlling antirheumatic therapies (DC-ARTs) should not be used for the treatment of soft tissue rheumatic disorders or osteoarthritis.

B. Usage

Treatment with SADs should be initiated as soon as possible after diagnosis of chronic inflammatory arthritis before significant damage to the joints has taken place. Choice of the individual agents to be used depends on the prescriber but should take into account the therapeutic ratio of the SAD in that particular clinical situation. The health care worker monitoring a patient on a SAD should be fully conversant with the known adverse reactions to that particular SAD. Criteria for response to a SAD include a decrease in clinical features (joint count, pain, duration of stiffness) and blood tests such as ESR, C reactive protein and other acute phase reactants. SADs are used in an attempt to prevent progressive disability and the development of cartilage and bone erosions.

C. Toxicity

Toxicity monitoring will depend on the SAD used - refer to the background paper. Further studies looking at the cost-effectiveness of various drug monitoring regimens need to be carried out. Studies reviewing differences in patient response and adverse reactions between different countries should be encouraged.

D. Therapy Cessation

Patients on SADs need frequent review to assess efficacy of therapy. If the SAD is not working, or if side effects occur treatment should be reviewed.

E. Patient Advice

Patients should be provided with a list of the common side effects and should be encouraged to

report to their health care worker if they have concerns about their treatment.

V.4 Corticosteroids

A. Indications for Use

Corticosteroids are extremely useful to control severe systemic connective tissue disease and vasculitis and may be used in active inflammatory joint diseases. They should not be prescribed for patients with osteoarthritis or soft tissue rheumatic diseases. They should always be used in the lowest dose possible to control disease and particularly in children where growth can be significantly retarded.

B. Usage

Corticosteroids can be given orally (prednisilone or prednisone) or parenterally (IV, IM, IA or intralesionally). Oral preparations with 1 mg tablets should be used to allow for small reductions in dose. Sale of preparations containing corticosteroids with other agents (ie, NSAIDs) should not be allowed. Control of severe connective tissue diseases (SLE, Vasculitis) may require high doses of oral or intravenous steroids initially. Dose should then be reduced to the lowest dose required to control the disease.

C. Toxicity

Corticosteroids are a major cause of adverse drug reactions when prescribed long term or in high doses. Particular care should be exercised with use of steroids in the young and in the elderly. Consideration should be given to use of calcium supplementation and hormone replacement therapy for those at particular risk of osteoporosis. Those patients on long term corticosteroids should be given steroid support in emergency situations, trauma or surgery.

Further studies identifying those at particular risk of corticosteroid side effects and strategies to reduce these should be considered.

D. Therapy Cessation

The doses of corticosteroids should be tapered as the disease process is controlled. Other SADs or immunosuppressive agents should be used as 'steroid sparing' agents where steroid dose produces unacceptable side effects without disease control.

E. Patient Advice

Patients should be encouraged to wear some type of identification that they are on long term steroids.

V.5 Hypouricaemic Agents

A. Indications for Use

Recurrent gouty arthritis, renal calculi, and tophaceous gout. Drug treatment of asymptomatic hyperuricaemia is not usually necessary.

B. Usage

Non-pharmacological methods (diet, weight reduction, stopping thiazide diuretics, etc.) should be pursued in addition to hypouricaemic therapy. Allopurinol can be used as a single daily dose. Uricosurics may require alkalinisation of the urine. Cost factors in long term therapy need to be appreciated. When commencing treatment with drugs which alter plasma urate concentration, patients should always be given colchicine (0.5 mg, BD) or an NSAID for at least 4 weeks to prevent acute attacks of gout.

C. Toxicity

Dosage of allopurinol should be reduced in patients with significant renal disease.

D. Therapy Cessation

Therapy should be reviewed if significant reduction in serum urate is not achieved.

E. Patient Advice

Patients should be advised that life time therapy is probably required. Further studies on intermittent dosage regimens should be pursued.

ANNEX VI:

PROTOCOL FOR TESTING SM-ARDS(NSAIDS)

The principal clinical effects of a nonsteroidal antiinflammatory drug (NSAID) are to reduce pain and inflammation. The difficulty is often how this is assessed, and great care has been taken in developing criteria for evaluation of end-points. Most endpoints are subjective and it therefore may be difficult to discriminate between the analgesic and antiinflammatory effect. NSAID are quick acting and maximum efficacy is usually obtained within 2 weeks. Some of the long half life NSAID might, however, take longer to reach steady state concentrations (particularly in joint tissues) and, therefore, sufficient time should be given to take this into account when assessing efficacy. This is usually of the order of 1 month.

NSAID may be tested in the following groups of rheumatic diseases: (1) Inflammatory diseases of the joints, of the extremities and spine, including rheumatoid arthritis (RA), seronegative spondyloarthropathies and related conditions, other systemic connective tissue disorders. (2) Certain metabolic joint diseases, e.g., gouty arthritis or calcium hydroxyapatite or pyrophosphate disease. (3) The inflammatory component of degenerative arthropathies, involving the joints of extremities and spine. (4) The inflammatory component of soft tissue or nonarticular rheumatism, including diseases of muscles, tendons, tendon sheaths, painful conditions of muscles caused by postural, occupational or other factors. (5) Pain models to investigate analgesic effect, i.e., dental pain, postepisiotomy or other postoperative pain, and pain of osteoarthritis (OA).

Ethics. All drug trials should be conducted in accordance with the Declaration of Helsinki. Before undertaking a trial of a new drug for the treatment of diseases, it is important to consider whether the drug in question is likely to offer any advantage over drugs already available. This applies particularly to NSAID, as there are already a considerable number.

Objectives. Studies of NSAID should be planned to establish in the short and longterm: (1) efficacy (relief of pain and stiffness and improvement in function), (2) safety, (3) relative efficacy and safety, the trial drug being compared to at least one reference drug, and, (4) the mode of action.

The types of trials. The characteristics of the disease to be treated should be considered in the design of the clinical trials, i.e., rapid fluctuations in disease activity, slow progressive disease, stable disease, etc., or acute arthritis, e.g., gout, or chronic disease, e.g., OA. Studies can be conveniently classified into four phases - the phases recognized for the purpose of this document are: Phase 1 - Initial studies in humans (human pharmacology); Phase 2 - Pilot therapeutic trials and dose finding studies; Phase 3 - Main therapeutic trials; and Phase 4 - Longterm studies (for safety) or special investigations, e.g., extremes of age, interactions, etc.

Background information on the trial drug and its anticipated relevance in treatment, as well as the objectives and anticipated problems of the trial, should be set out when the study is designed.

The patient sample should be as homogeneous as possible and any subgroups identified. If it is likely that these subgroups will respond in a different way, then they should be stratified. There must be a requirement for drug treatment. The possible effects of non-drug therapy (physiotherapy, surgery, immobilization, etc., or changes in lifestyle with possible therapeutic influence) should be taken into account in the design of the studies.

Initial studies in humans. These usually comprise initial investigations on a few healthy volunteers or on a small number of hospital patients, in order to confirm the findings of animal experiments, to obtain initial data on pharmacokinetics, and to determine the approximate dose.

Pilot therapeutic trials and dose finding studies. These investigations involve a large number of patients,

and are often carried out as open studies on patients in hospital. They are designed to obtain reliable basic data on matters described in the following Table.

Pharmacokinetics and pharmacodynamics

- Presence of a therapeutic effect - this might involve the first comparison with a placebo. These early placebo controlled trials should be at least 6 weeks' duration and use of acetaminophen should be allowed, recorded, and used as a measure of efficacy.
- Dose response and dose ranging studies; these should be (1) placebo controlled; (2) involve cohorts of patients who are assigned a particular dose and stay on it for the duration of the trial; (3) not involve complex dose titration regimens that are difficult to interpret or analyze (dropouts for any reason should be noted and reported).
- Elderly patients should be included if the drug is likely to be used in this age group.
- An impression of the potential indication for use of the drug.
- Principal short term adverse reactions to the drug. These should include blood loss studies using labelled chromium and endoscopic studies.
- Major reasons for nonresponse.
- Possible interaction with other drugs, particularly anticoagulants, anticonvulsants, and antihypertensive agents.
- Possible interaction with other interventions (surgery, physiotherapy, lifestyle change, etc.)

Major therapeutic trials. Before starting these trials, there should be critical appraisal of work in the earlier phases to ensure there is a therapeutic effect, and that this (and the effects observed on laboratory variables) justifies further studies. Requirements of the main trials are described in the next Table.

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- Controlled studies with a sufficient number of patients to reach statistical significance and to avoid type 1 error (i.e., the risk that a difference that is indeed present between 2 groups will not be demonstrated). The dose range of the trial drug believed to be optimal should be employed.
- Comparison with active reference drugs (and perhaps further placebo trials) within appropriate dose ranges in relation to the response curve of the trial and the reference drug.
- Study of individual preferences (in crossover studies only).
- Controlled withdrawal studies (where appropriate).
- Longterm studies, provided a reasonable number studies (i.e., 100 for 1 year and 500 for 6 months), and special studies.
- Further studies (including postmarketing evaluation and surveillance).
- Continued controlled trials to broaden knowledge of the therapeutic effect, indications, and adverse reactions.
- Trials for new indications.
- Studies in special subgroups of patients, e.g., elderly patients (> 65 years), diabetics, children, and other groups at special risk. This may include pharmacokinetic and pharmacodynamic studies in patients with renal, hepatic, cardiac insufficiency.
- Longterm efficacy and safety studies, which, in chronic disease, are of particular importance in view of possible fluctuations in the disease and the longterm effects (wanted or unwanted) of prolonged drug treatment. Longterm safety studies can be open, but it is obviously of medical importance to determine how safe a drug is compared with others of its type.
- Benefit/risk and benefit/cost analysis are encouraged.

Selection of patients. Clear diagnostic criteria of the conditions under study should be set out and fulfilled by patients entering the trial and should include age, sex, weight, height, and the main characteristics of the disease. Disease complications and concurrent treatment should be recorded so their effects, if any, on the results of treatment with a new drug may be determined. In view of the age structure of the rheumatic population, it is particularly important that elderly patients be studied from an early phase, both in kinetic and therapeutic investigations.

Clinical trial design. The nature and specific uses of various study designs can be summarized as follows:

Open study. Both the patient and the doctor know which drugs are in use throughout the trial. These studies are of limited value for demonstrating efficacy, primarily because of the biases that influence assessments.

Single blind study. Either the doctor or the patient knows which drugs are being used in each case. An alternative is the use of an independent blinded observer.

Double blind study. Neither patient nor doctor know which drug, active or placebo or reference, is given during the various phases of the trial. An alternative is the use of an independent blinded observer.

Triple blind study. Assessor, doctor, and patient are unaware of the treatment.

It is important for the person doing the outcome assessment to be blinded, particularly where the measurement process can be affected by the person doing the measurement. An ideal trial should have all those involved in the trial blind to the treatment.

Controls. Stratification may also be required if there is wide variation in the patient material. When choosing treatment for the control group, it should be decided whether it is desirable or ethically justifiable to use a placebo or whether another active (reference) drug should be used for comparison.

In all comparative studies, patients should be randomly allocated to receive the active compound or the placebo (reference drug). Special tables for randomization are available. The randomization should take place after patients are accepted for the trial.

Controls can, in principle, be of two types: (1) Controlled trials with a parallel group; random allocation is essential and double blinding techniques should be applied. (2) Crossover designs, in which patients serve as their own controls.

Crossover trials are mainly useful for drugs with a short half life or a short duration of effect, and where the effect is reversible. If this is not the case, carryover effect might invalidate the results. Consideration should also be given to the possibility of the difference in the carryover effect between the two drugs. The desirability or necessity for a washout period before entering the trial, and between the different phases of the crossover study, will depend on the carryover effect of drugs involved in the trial and of any drugs taken in advance. In crossover studies, the order of administration of drugs should be randomized since it might affect the outcome, e.g., if the first drug produces a greater placebo effect. The advantage of a crossover trial is that the drug effects can be compared within patients, and this variation is generally smaller than between-patient variation.

Where these criteria for performance of a valid crossover trial cannot be met, preference should be given to comparative parallel between-patient studies.

Importance of selecting patients with diseases responsive to NSAID. In inflammatory forms of arthritis such as RA or the seronegative arthropathies where patients are already taking NSAID, a flare in disease (predetermined increase in clinical characteristics such as joint count, pain score, or duration of morning stiffness) should be demonstrated by substituting placebo for their usual NSAID therapy before they enter the trial. Patients would be given analgesic for pain and enter the study as soon as a flare in symptoms is evident. Only patients who demonstrate a flare in disease activity should be admitted to the study and they would, therefore, be randomized to receive placebo or active compounds. In the ideal situation, a similar substitution of placebo should be carried out at the end of the trial to demonstrate that the patient has had responsive disease throughout the study period. Timing of the placebo flare should be organized to

minimize the duration of the flare, and rescue analgesics provided to minimize the increased pain.

Multicenter trials. These are often necessary to obtain a sufficiently large number of patients within a short period. In a multicenter trial, the selection of patients and the collection of data are carried out by a number of physicians. The number of patients from each centre should be fairly similar and should be sufficient to exclude potential biases. A multicenter trial introduces certain difficulties regarding the comparability of patients, as well as introducing observer differences. But these failures can be compensated for in the design, and in particular by stratifying by center.

Treatment schedules and dosage. The dosage schedule should be specified and explained in advance. Detailed instructions should be given. There should be a well defined design for changes in doses during the trial, if indicated. Fixed dose increments or individual dose titration may be necessary in pilot studies, or even in major clinical trials. The time of intake of the drug in relation to meals should be known and recorded. Any reference drug (used as a control) should be given at the accepted therapeutic dose, so comparisons of efficacy and safety can be valid.

Endpoints. A wide variety of clinical endpoints can be used in trials of NSAID. They should, however, fulfil the following criteria and the guidelines suggested by the recent OMERACT meeting.

Criteria for Evaluating Indices for Musculoskeletal Clinical Trials

1. The index should be designed for a specific purpose.
2. The index should be validated on individuals or populations of patients having similar characteristics to study populations.
3. Reliability should be adequate for achieving measurement objectives.
4. Validity (face, content, criteria, and construct) should be adequate for measuring objectives.
5. The index must be responsive (i.e., able to detect significant change in the underlying variable).
6. Index performance should be maintained in subsequent applications under similar study conditions.
7. The method of deriving scores, particularly in composite indices, should be credible and comprehensible.
8. The feasibility of data collection and instrument application should not be constricted by time or cost.
9. The measurement process must be ethical.
10. The index should also be adopted by other clinical investigators.
11. The influence on the endpoints of language, cultural differences, and other factors should be appreciated.

The following endpoint measurements can be used in trials of NSAID. (1) Pain: Likert scale, visual analogue scale, numerical rating scale, graphic rating scale, continuous chromatic analogue scale, and pain face scale. Behavioral observation methods can also be used, as well as questionnaires (McGill or analgesic consumption). (2) Joint count: articular index (Lansbury index, ARA Cooperating Clinics index, Ritchie index for RA, Doyle index). (3) Global assessment, use of signal measurements, i.e., signal joints or signal functions. (4) Functional indices and quality of life measures, arthritis status index (FSI), health assessment questionnaire (HAQ, Mactar AIMS 2, and the WOMAC). (5) Joint stiffness: duration or visual analogue scale. (6) Performance tests: grip strength, duration of 16 meter walking time.

The preferred outcome measures in clinical trials in RA and OA have been noted by workers in this field, and more recently for RA by the OMERACT group.

For RA (top 9 ratings): joint count, pain (change), global activity (absolute), joint stiffness, grip strength, 16 meter walking time, joint swelling, ESR, and quality of life measures. For function (top 5 ratings): self care, physical activity - mobility, pain, role activities, and mental health. For OA (top 13 ratings): pain, patient global assessment, range of movement, physician global assessment, joint stiffness, qualitative aspects of sleep, walking time, activities of daily living, joint tenderness, analgesic consumption,

joint swelling, signal joints, and quality of life measures.

To this list should be added a global activity measure from both the viewpoint of the patient and the physician, and if the study progresses for more than 1 year, radiographs should also be viewed.

It is now appreciated that a few high quality measures and a set of 4-6 measures of inflammatory activity are probably more appropriate.

Before any clinical studies are undertaken, investigators should decide what degree of response will be regarded as clinically useful.

With investigations of drugs used in rheumatic diseases, it is particularly important not to place excessive weight on objective responses compared to well validated subjective responses - the latter might be a more sensitive indication of the patient's well being. Measurements should be standardized, as far as possible, and ideally be undertaken by the same investigator and at the same time of day on each occasion. All tests should define exactly how measurements should be made and how questions should be asked. This is especially important in multicenter trials, where differences in approach between the various centers can easily occur. Questions put to patients should be standardized, with an alternative way of asking each question if at first it is not fully understood.

Sample size tables for most of the rheumatic diseases have recently been produced.

Withdrawal from the trial (Because of adverse reactions, lack of effect, or lack of patient co-operation). The reason for all deliberate withdrawals and dropouts should be clearly recorded. They should be scored as failure of/or intolerance to the trial drug, and included in the statistical analysis if they are clearly unrelated to therapy, e.g., intercurrent illness or injury, secondary exclusion, or migration.

Adverse reactions to side effects. Adverse reactions and side effects observed by the investigator and elicited from the patient in response to the question "How is/are the medicine(s)/tablet(s) suiting you?" should be recorded. In addition, all medical events occurring during the trial, even if not apparently related to the trial drug, should be recorded.

Measures to monitor compliance. Compliance can be checked during the trial by asking the patients, by counting the remaining tablets, or by monitoring plasma drug levels or urine metabolites. The methods used should be stated in the protocol and it is commonly advisable to employ more than one.

Exclusion of patients. General principles applicable to the exclusion of patients, e.g., pregnant women, are as for investigations of other classes of drugs, but some special consideration might be applicable.

Statistical consideration. Statistical advice should be taken early in the planning stage of a trial. (1) To determine the number of patients who should take part in the study to achieve statistically significant discrimination; the number of patients can be precalculated using recognized formulae. (2) To determine the number of patients required to demonstrate any lack of clinically relevant differences between the 2 methods of treatment. In that case there should be agreement between the physician and the statistician on the power of the statistical test.

The data should be analyzed on an intention-to-treat basis, i.e., all patients randomized should be included in the statistical analysis.

Organizational aspects, i.e., obtaining informed consent, are very important and ideally patients should be given a copy of the informed consent form. The informed consent form should be written in language understandable by the patient and should include a list of adverse effects the patient may experience.