LANDMARK DIAGNOSTIC TESTS

- Rose-waller
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- ANTI-CCP
EXTENDED REPORT

Diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis

I Vallbracht, J Rieber, M Oppermann, F Förger, U Siebert, K Helmke


Objective: To assess the additional diagnostic and clinical value of the second test generation of anti-cyclic citrullinated peptide antibodies (CCP2) compared with rheumatoid factor isotypes (IgG-RF, IgA-RF, IgM-RF) in patients with rheumatoid arthritis.

Methods: This was a prospective study on 715 patients: rheumatoid arthritis (n = 295), degenerative or other inflammatory joint disease (n = 163), connective tissue disease or vasculitis (n = 103), and healthy controls (n = 154). Sera from each subject were tested for CCP2 and RF isotypes by enzyme linked immunosorbent assay (ELISA). Agreement with clinical indices such as disease activity, joint destruction, disease duration, and other laboratory tests was assessed. Sensitivity and evaluated taking the clinical diagnosis as the gold standard.

Results: Highest sensitivity was found for IgM-RF (66.4%) and CCP (64.2%) achieved by CCP (97.1%) and IgG-RF (91.0%). In rheumatoid patients with higher joint damage, CCP was more often present (81.4% and 83.6%) than all RF isotypes. The value was the detection of positive CCP in 34.5% of all patients with measured RF isotypes (IgG-RF, IgA-RF, and IgM-RF) were negative.

Conclusions: As a screening method for rheumatoid arthritis the IgM-RF and to other RF isotypes. Positivity in the highly specific CCP ELISA supports arthritis. CCP proved to be a powerful diagnostic tool, especially in amb patients with rheumatoid arthritis.
Dr Jacques Forester, the pioneer of gold
RHEUMATOID ARTHRITIS AND ITS TREATMENT BY GOLD SALTS

JACQUES FORESTIER, M.D.
Paris, France

From the Hopitaux de Paris and the Hospice Thermal Reine-Hortense, Aix-les-Bains

Reprinted from THE JOURNAL OF LABORATORY AND CLINICAL MEDICINE
St. Louis

Vol. 20, No. 8, Page 827, May, 1935

(Printed in U.S.A.)
A CONTROLLED TRIAL OF CYCLOPHOSPHAMIDE IN RHEUMATOID ARTHRITIS

Cooperating Clinics Committee of the American Rheumatism Association

Abstract Cyclophosphamide was given for 32 weeks to 48 patients with severe active rheumatoid arthritis. Twenty received a high dose (up to 150 mg daily), and 28 a low dose (up to 15 mg daily).

In comparison to the low-dose group, the high-dose patients showed greater reduction in disease activity in five of the six measures evaluated, in the assessments of both physicians and patients, and in the summing of changes in individual patients.

More of the high-dose patients had reductions of rheumatoid factor titer and of serum immunoglobulin G. A unique reduction in hand-joint erosions was found on x-ray study in the high-dose group. The clinical response was not related to leukopenia or to specific white-cell depressions.

Untoward effects were observed in 90 per cent of the high-dose and 40 per cent of the low-dose groups. Herpes zoster, cystitis and major hair loss were virtually confined to the former.
Efficacy of Low-Dose Methotrexate in Rheumatoid Arthritis

Michael E. Weinblatt, M.D., Jonathan S. Coblyn, M.D., David A. Fox, M.D., Patricia A. Fraser, M.D., Donald E. Holdsworth, M.D., David N. Glass, M.R.C.P., and David E. Trentham, M.D.

Abstract Twenty-eight patients with refractory rheumatoid arthritis completed a randomized 24-week double-blind crossover trial comparing oral methotrexate (2.5 to 5 mg every 12 hours for three doses weekly) with placebo. The methotrexate group had significant reductions (P<0.01 as compared with the placebo group) in the number of tender or painful joints, the duration of morning stiffness, and disease activity according to physician and patient assessments at the 12-week crossover visit; reductions in the number of swollen joints (P<0.05) and 15-m walking time (P<0.03) also occurred. These variables, as well as the grip strength and erythrocyte sedimentation rate, showed significant (P<0.01) improvement at 24 weeks in the population crossed over to methotrexate.
Retardation of Joint Damage in Patients With Early Rheumatoid Arthritis by Initial Aggressive Treatment With Disease-Modifying Antirheumatic Drugs

Five-Year Experience From the FIN-RACo Study

Markku Korpela,¹ Leena Laasonen,² Pekka Hannonen,³ Hannu Kautiainen,⁴ Marjatta Leirisalo-Repo,² Markku Hakala,⁵ Leena Paimela,⁶ Harri Blåfield,⁷ Kari Puolakka,⁸ and Timo Möttönen,⁹ for the FIN-RACo Trial Group

Objective. To evaluate the long-term frequency of disease remissions and the progression of joint damage in patients with early rheumatoid arthritis (RA) who were initially randomized to 2 years of treatment with either a combination of 3 disease-modifying antirheumatic drugs (DMARDs) or a single DMARD.

Joint damage seen on radiographs of the hands and feet obtained annually up to 5 years. Radiographs were assessed by the Larsen score.

Results. A total of 160 patients (78 in the combination group and 82 in the single group) completed the 5-year extension study. At 2 years, 40% of the patients in
Pyramid Approach to RA Treatment

- NSAIDs
- DMARDs
- Combination DMARDs
- Experimental drugs/procedures
- Corticosteroids

Multidisciplinary team

Mild-to-moderate RA

Severe RA
Modified Pyramid Approach to RA Treatment

NSAIDs

DMARDs

Combination DMARDs

Experimental drugs/procedures

Mild-to-moderate RA

Severe RA
# Poor Man’s Cocktail for RA

- Hydroxychloroquine.... 1
- Sulfasalazine.... 2
- Methotrexate.... 3 1
- Leflunomide..... 4
Editorials

Suppress Rheumatoid Inflammation Early and Leave the Pyramid to the Egyptians
D.J. McCarty

Comment
Winning the Battle, Losing the War?
Another Editorial About RA
J.H. Klippel
Historical Note

Fifty Years of Cortisone

In 1949, just over 50 years ago, I was a young Fellow (the first in rheumatology) at Columbia-Presbyterian Medical Center in New York. At the annual meeting of the American Rheumatism Association (ARA) that year, Philip Hench presented the seminal work on the first use of Compound E (cortisone) in rheumatoid arthritis (RA), illustrated by a before-and-after movie of a severe rheumatoid attempting to climb stairs and failing and then skipping up them the day after receiving an injection of corticosteroid. The entire audience stood and cheered as this was recognized to be a major development. Hench and Kendall (along with the Swiss, Reichstein) received the Nobel Prize. The paper presented and subsequently published bore the names of Hench and Kendall, along with Charles Slocumb and Howard Polley who had done the actual clinical work.

One of the important tests of a discovery is that it must stand the test of time. Although corticosteroids did not turn out to be the panacea for which everyone hoped, few can deny that they occupy an important place in medical therapeutics over 50 years from the first clinical observations. Not only that, but their introduction has led to a vast field of Head of Section of Rheumatology (1960), and Professor of Medicine (1962). He was the first Chairman of the Division of Rheumatology (1966) at the Mayo Medical School, where he was later appointed Professor of Medicine (1973).

Following his retirement from the Mayo Medical School in 1983, Howard was appointed Professor of Medicine at the Indiana University School of Medicine. In 1989 he returned to Rochester, where he remained until his death.

As the junior member of the Mayo Clinic team of Philip Hench, Edward Kendall, Charles Slocumb and Howard Polley, Howard was responsible for many of the earliest clinical observations relating to treatment of RA with cortisone. Their paper describing the effects of cortisone in patients with RA was given in 1949 at the New York combined meeting of the ARA and the 7th Congress of the International League Against Rheumatism (ILAR). Its superb slides and cinema were truly dramatic. This paper was and remains a critical landmark in rheumatology. In 1951, Howard received a special citation from the ARA “for his participation in the clinical discovery of cortisone.”

In 1954, Howard, with Emerson Ward, co-founded the
STEROIDS

- When, Which, How, How long
- Prednisone, Methyl prednisone Succinate / Acetate
- Oral, IM, IV, IA
- Step up, Step down
- Divided doses / Once daily / Alternate day / Stat / Pulse
- Effects Vs Side effects Cotherapy
- Calcium, PPI, Antibiotics, Antidiabetics
"PHARMACOLOGY IS THE SCIENCE OF SELECTIVE TOXICITY"

- Adrian Albert, 1906
What Pavlov would have used if he hadn’t had a bell.

Why experiment with dry mouth therapies? For proven response in xerostomia, trust Salagen Tablets. It's the only therapy that offers dependable efficacy for the symptoms of xerostomia caused by both Sjögren's syndrome and radiation therapy for head and neck cancer. That efficacy is backed by nearly a decade of clinical experience and more than 18 million patient days of therapy.* Plus a safety profile with no surprises. Salagen Tablets offer excellent tolerability with a low incidence of GI side effects and a discontinuation rate comparable to placebo at the recommended dose.\(^{1,4}\)

With reliability like this, why experiment? Trust the proven choice.

Salagen Tablets do not work for everyone and are contraindicated when uncontrolled asthma is present and when miosis is undesirable. The most common side effect is sweating. Although less frequent, other side effects may occur (eg, chills, flushing, headache, and frequent urination).

Please see brief summary of Prescribing Information on adjacent page.

*Based on total prescriptions dispensed and total dose.
Mouth-watering relief

EVOXAC® first line—proven relief for the dry-mouth symptoms of Sjögren’s syndrome

Patients treated with EVOXAC reported significant improvement for the following end points:

- Feeling of mouth
- Dryness of mouth
- Dryness of tongue
- Ability to speak without drinking liquids
- Ability to chew and swallow food
- Ability to sleep

EVOXAC® (cevimeline HCl) Proven Relief... Proven Results
TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases

Marc Feldmann and Ravinder N Maini

From immune regulation, through soluble mediators, to autoimmunity (Marc Feldmann)

As a medical student in the late 1960s in Australia, I realized that we knew very little about the mechanisms of disease, and I was eager to learn more. In Melbourne, the premier research institute was the Walter & Eliza Hall Institute (WEHI) of Medical Research, led by the dynamic Gustav Nossal. I began my PhD studies developing the then novel method of immune cell culture, under the supervision of Erwin Diener and Gus Nossal. I used this new approach to investigate mechanisms of immune regulation, with a particular interest in the soluble mediators of immunity, which were subsequently characterized and cloned as cytokines. This interest grew during my postdoctoral research at the Imperial Cancer Research Fund Immunology Unit. At the time no immune responses had been detected to human cancers, so I thought that an approach to generate them might be learned by studying the pathogenesis of human autoimmune diseases, an interest I had acquired at WEHI. In these diseases, immune responses to self tissues do occur, paradoxically, despite the protective role of the immune system. I started by analyzing thyroid diseases, and from this study in the early 1980s I realized that cytokines were likely to be of major importance in their pathogenesis. To study autoimmune tissue and its molecular mediators at the height of the disease was not possible for thyroiditis, but was possible for rheumatoid arthritis, which can be sampled at the height of the disease. I therefore arranged to meet Ravinder Maini, and a fruitful collaboration ensued (Fig. 1).
Disease Progression

Early Rheumatoid Arthritis
- Neutrophils
- Hyperplastic Synovial Membrane
- Capillary Formation
- Hypertrophic Synoviocyte

Established Rheumatoid Arthritis
- Neutrophils
- Plasma Cell
- Synovial Villi
- Extensive Angiogenesis
- Eroded Bone
- Pannus

Normal Joint
- Bone
- Cartilage
- Capsule
- Synovial Membrane
- Synoviocytes

Adapted with permission from: Choy EHS, Panayi GS. *N Engl J Med.* 2001;344:907-916. © 2001 Massachusetts Medical Society. All rights reserved.
Soluble Receptor Constructs Bind and Neutralize Soluble TNF-α and TNF-β, but Not Membrane-bound TNF-α
The Role of TNF-\(\alpha\) in RA Pathology
Activated Th1 Cell in Rheumatoid Arthritis

Th1 cell

IL-2

IFN-γ

TNF-α

Ankylosing Spondylitis: The Facts

• Shortens life expectancy

• Does not burn out

• Not milder in women

• Adversely affects employment

• Not very rare disease
Frequency Distribution:
Age of Onset & Age of Diagnosis

Calin et al.
Inhale CO$_2$ / Exhale O$_2$

Inhale O$_2$ / Exhale CO$_2$
Daily ups and downs of body rhythms

- Body temperature (°F)
- Systolic blood pressure (mm Hg)
- Cortisol hormone secretion (μm/dl)
Inflammation

Cytokines

Hypothalamus

CRH

Pituitary

ACTH

Cortisol

Adrenal

Nadir

Peak

Time of day

- Plasma cortisol levels**
- Plasma prednisolone levels***
STEROIDS

• Which, How, How long
• Prednisone, Methyl prednisone Succinate / Acetate
• Oral, IM, IV, IA
• Step up, Step down
• Divided doses / Once daily / Alternate day / Stat / Pulse
• When ?
Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis.

Practical clinical pharmacology and drug interactions of low-dose methotrexate therapy in rheumatoid arthritis.

- Furst DE.

Bioavailability of higher dose methotrexate and subcutaneous administration.

Pharmacology and pharmacokinetics of methotrexate in rheumatic disease. Practical issues in treatment and design.

- Hillson JL.
- Furst DE.

Arthritis Clinical Research Unit, Virginia Mason Medical Center, Seattle, Washington, USA.
Methotrexate (MTX) is among the most effective drugs for treatment of rheumatoid arthritis and has been proven valuable in the treatment of multiple other disorders of immune regulation. MTX has been administered at a wide range of doses and dose regimens.

[Pharmacokinetics of methotrexate in rheumatoid arthritis: therapeutic implications]

- Bannwarth B, Pehourcq F, Lequen L.

Section of oral methotrexate (MTX) absorbed 10 mg/m².


Schroder H.
Department of Pediatrics, Aarhus Kommunehospital.

The author has performed in vivo investigations of the methotrexate (MTX) accumulation, kinetics and polyglutamate metabolism in erythrocytes, neutrophils and myeloid bone marrow cells during clinical MTX therapy of patients with acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma and psoriasis. On the basis of these studies the clinical applicability of monitoring erythrocyte MTX concentrations in children with ALL and adult psoriasis patients have been evaluated. To accomplish this task a set of methods has been developed: 1) An automated enzymatic assay adapted for a centrifugal analyzer was used to measure MTX concentrations between 10 and 60 nmol/mL.
Splitting high-dose oral methotrexate improves bioavailability: a pharmacokinetic study in patients with rheumatoid arthritis.

- Hoekstra M,
- Haagsma C,
- Neef C,
- Proost J,
- Knuif A,
- van de Laar M.

CONCLUSION:
The bioavailability of oral higher dose MTX in adult patients with RA can be improved by splitting the dose.

• MTX : half life / frequency
Active Disease Despite Methotrexate: ACR 20 Responses*

*All patients were on baseline methotrexate
Time to Efficacy or Toxicity Failure by Treatment (62)

Log-rank test: \( P < 0.001 \)
COBRA combination therapy in patients with early rheumatoid arthritis
Leflunomide Blocks T Cell Clonal Expansion

Resting T Cell

Activation

$G_0$

Activation

$G_1$

Leflunomide

$S$

Clonal Expansion
Clinical Implications

• Loading dose:
  - After 3 days: effective conc 13 mg/L.
  - 4 weeks, if no loading dose.

• Plateau effect, after loading dose
  - Higher doses does not enhance clinical success
Css(20 mg): Simulation Washout Phase, No Use of Cholestyramine

The vast majority of patients are clear of leflunomide after 12 months.
pK and Use of Cholestyramine

after 3 weeks ≈ 90% of patients below tox threshold of 0.02 mg/L
The Chronopharmacology of Penicillamine. This diagram depicts the peak incidence of some of the more common side effects of penicillamine during a course of therapy with a maintenance dose of 1 g/day. Most of the serious reactions will have developed during the first 18 months of treatment. Aplastic anemia was not included in this illustration, but it may occur at any time, particularly after an increase in dosage. (After Balme HW, Huskisson EC: Chronopharmacology of penicillamine and gold. Scand J Rheumatol 4(Suppl 8):21, 1975.)
Biologicals
Time Course of Action / Dosage Frequency

- **Infliximab**: Day 0, 14, 60
- **Anakinra**: Daily
- **Etarnecept**: Twice / once in a week
- **Adalimubab**: Twice a month
- **Abatacept**: Once a month
- **Golimubab**: Once a month
The Saga of Medicine: A story of 150 years and beyond

Man-Microbe relationship...

Louis Pasteur  Antonius van Leeuwenhoek  Robert Koch  Paul Ehrlich

...Infection & Immunity: Friends or Foes?
Every CV Disorder: Autoimmune disease!

Every Autoimmune disease: infectious?!!!
Infection & Immunity: Friends or Foes

- Era of vaccinations
- Staph aureas arthritis
- Rheumatic fever
- RA, SSA, SLE
- APS
- TB / HIV / Hepatitis C
# APS Etiology

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>cardiolipin</th>
<th>β2GPI</th>
<th>APS manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>IgG</td>
<td>+</td>
<td>Thrombosis, brain infarction</td>
</tr>
<tr>
<td>EBV</td>
<td>IgG, IgM</td>
<td>+</td>
<td>PE&lt;sup&gt;a&lt;/sup&gt;, thrombosis</td>
</tr>
<tr>
<td>Varicella</td>
<td>IgG, IgM</td>
<td>─</td>
<td>PE, thrombosis</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>IgG</td>
<td>+</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>B19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>IgG, IgM</td>
<td>+</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>IgA</td>
<td>─</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HIV</td>
<td>IgG, IgM, IgA</td>
<td>+</td>
<td>Leg ulcer necrosis, PE, VE&lt;sup&gt;c&lt;/sup&gt;, arterial &amp; vein thrombosis, vasculitis, livedo reticularis</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>IgG</td>
<td>+</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pulmonary embolism

<sup>b</sup> Not determined

<sup>c</sup> Venous embolism
Antiphospholipid syndrome

Infectious origin of the antiphospholipid syndrome*

Y Shoenfeld, M Blank, R Cervera, J Font, E Raschi, P-L Meroni

From a systemic disease towards the infectious aetiology

The general consensus is that autoimmune diseases have a multifaceted epidemiology. The classical antiphospholipid syndrome (APS) is characterised by the presence of antiphospholipid antibodies. It is associated with the thrombosis, recurrent miscarriage, and neurological symptoms. However, the pathogenesis of APS is not fully understood.

β₂GPI independent and non-pathogenic antibodies, several later studies clearly documented their reactivity with β₂GPI.

Antibiotics in APS

In contrast with rheumatic fever or other infectious autoimmunity related conditions, in APS it seems that the disease is derived through two hit mechanisms (see later text)—that is, the infections might have occurred long before the autoimmune manifestation emerges. Thus, the infection is not always apparent in the case of APS. Yet, two reports point to the effectiveness of antibiotics in APS and especially in the catastrophic subtype. In the first of these reports, of a patient with APS associated with H pylori, all disease manifestations disappeared upon eradication of the bacteria. In the other—an experimental model of APS—the manifestations were abrogated by parallel treatment with ciprofloxacin.

THE CATASTROPHIC APS AND INFECTIONS

An unusual and potentially fatal subset of the APS was first defined in 1992: the catastrophic APS (c-APS) that is associated with a high risk of death and a devastating outcome.

Annals of the Rheumatic Diseases

JANUARY 2006 VOL 65 NO 1
TB

- WHO estimates
  - One third of world is infected
  - 2\textsuperscript{nd} leading killer disease
  - Frequent traveller
- In 90% infection remains latent
- 10% develop disease
  - Most in first 2 years after infection
  - Immunocompromised patient \uparrow
  - Immunosuppressive drugs\downarrow\uparrow
  - Multi drug resistance
- Lurking HIV
Latency in TB

- 95% of adults develop protective immunity following infection with M. tuberculosis.
- Despite robust response, the immune system is unable to completely sterilize host tissue.
- The bacteria can persist in by reduced metabolic activity i.e. latency.
- If cell mediated immunity is impaired, reactivation tuberculosis can develop decades after the initial infection.
PREVALENCE CASE CONTINUING
62% (0.62)

CASE PREVALENCE
INITIALLY
pto 1.0

ONE YEAR
-0.20 -0.18 +0.38
(-d-c+1)

NEXT YEAR
pto 1.0

Pool of tuberculosis cases in the community (natural dynamics).
Source: Ref. 14.
TB Symptoms

• Asthenia
• Weight loss
• Fever
• Cough
• Dyspnoea, haemoptysis
• Local signs (depending on the organ)
• Sweating
Protean Manifestations of TB

**Pulmonary**
- Pneumonitis
- Emphysema
- Bronchiectasis
- Pleural effusion
- Miliary
  - Acute
  - Cryptic

**Extra pulmonary**
- Lymphadenopathy
- Abdominal
- Meningeal
- Bone & joint
- Poncet's disease
- Erythema nodosum
TNF-α

- Response to TNFα mediated through receptors
- TNF receptor 1 (TNFR1)
  - Primarily binds soluble TNFα
  - Integral to granuloma formation and maintenance
- TNF Receptor2 (TNFR2)
  - Primarily binds transmembrane TNFα
  - Less important to granuloma formation
TNF-α

- TNF: ↑Grannuloma formation, ↓Mtb
- TNF blockade: latency to reactivation
- New strategy: Inflammation ↓↓↓
  Anti infection ↑↑↑↑
- Complex multi functional
- Infection – immunity affair
Risks of TNF-alpha-inhibition

- Infections
- Increased number of septic joints?
- Effects on healing of wounds?
- Local and Infusion-reactions
- Incidence of lymphoma/ carcinoma?
- Induction of Immunreactions
Interferon-γ

- Interleukin-12 Signal-Transduction Cascade

Lekstrom-Himes JA, Gallin JI. Immunodeficiency Diseases Caused by Defects in Phagocytes.
Osteopontine (Opn)

- Produced by macrophage and T cells
- Involved in modulation of IL-12
- Increased (Opn) production is a characteristic of Mt b granulomatous reaction
From Scallon, et al
Antibody cross-linking or membrane TNF-α activating complement and results in cell death

Macrophage with intracellular microorganisms (M. tuberculosis, Listeria, Salmonella)

Spread of Infection

Cell death and release of intracellular microbes or failure to kill intracellular organisms
Diagnostic Dilemmas

- Immunocompromised patient: RA, SLE, ± APL
- Rx: Cytotoxics, steroids
- H/o TB / old fibrotic lesion
- Mantoux: BCG+, Anergy
- Latent TB: primary, secondary
- Pulmonary, extra pulmonary / lymphadenopathy, miliary, abdominal
- Poncet's disease
- Investigations: Systemic, organ specific, imaging, biopsies, newer tests
- AIDS
Diagnostic Dilemmas…

• 39yr M: Severe backache, stiffness, oligoarthritis, pyrexia, parasthesiae lower limbs
• X ray/MRI: mild compression L1- L2:
• Disc ? AS ? Koch’s?
• Unresponsive to NSAIDs, steroids
• Calculated risk taken, remarkable recovery with biological
• INH prophylaxis
Diagnostic Dilemmas...

- 42yr F Crippling RA, ILD, CRF,
- Unresponsive to Mtx
- Old lesions of Koch’s, Mantoux negative
- Radical remission with biological
- INH prophylaxis
SLE ± TB

- DMARDs
- Steroids
- Cytotoxics
- Anti-Kochs
- Biologicals (Rituximab, Infliximab)
HIV related tuberculosis (n=8640)

- TB Incidence: 93.5%
- Pulmonary: 75.5%
- Extra pulmonary: 43.5%
- Disseminated: 14.5%

JK Maniar, Interim data, Jaslok & Somaiya Hospitals, Mumbai India
INVITED ARTICLE

Evidence-based practice in rheumatology
Prakash K. PISPATI

INTRODUCTION
It is so fashionable these days to discuss evidence-based medicine (EBM). But what is EBM? It can be defined as clinical expertise informed by the best available evidence obtained from systematic research.¹

EPIEMIOLOGY: A LONG WAY TO
How often one comes across lay statements
ARTHRITIS AND HOW TO CURE IT...
Manual of Rheumatology

Editor-In-Chief
P. K. PISPATI

2nd Edition
Pursuit of Knowledge, From Babel to Google
Thank You
Obrigado
Gracias
Thank You
Shukran
Merci
Arigato
Danke
Dhanyawaad