



Reflections on Modern Rheumatology
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Reflections on Modern Rheumatology

Cause for celebration and concern - David Pisetsky

I am honored to provide a commentary for the Voice of APLAR and will use this occasion to reflection the state of modern rheumatology from the perspective of almost 40 years of practice. My goal is to identify both the accomplishments and the challenges of our field. The advances in the treatment of rheumatologic disease have been astonishing and I believe that rheumatology has witnessed greater improvements in the clinical outcomes of its patients than any other medical subspecialty. Furthermore, these advances have come with therapeutic agents and approaches that have been relatively easier to administer and, fortunately, and perhaps surprisingly, do not have serious toxicity.

Gold therapy: more harm than good?

The most dramatic changes have occurred in the treatment of rheumatoid arthritis (RA). RA is the most common form of inflammatory arthritis, affecting as much as 1% of the population, with women outnumbering men. When I started my career, the options for

treating RA were limited. Our unit conducted a special clinic called the "Gold Clinic" where we administered either myochrysin or solganal. Because North Carolina, the state where I live, had very few rheumatologists in practice at the time, patients would travel long distances to seek subspecialty care. A journey of 100 or 200 miles was not unusual. For the clinic, the first thing we did was to obtain blood and urine to monitor for toxicity. The patients would then sit in the waiting room, chatting with each other or watching TV, until the results were back. If the platelet and white blood cell counts were in the healthy range and the urine free of protein, the patients would receive a shot in the buttocks and then make the long trip home.



Eminent Rheumatologist, Master ACR, USA

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Societal Impact of RA

Added dimension to a ubiquitous disease - Rohini Handa

Rheumatoid Arthritis (RA) has the distinction of being the commonest inflammatory polyarthritis seen in clinical practice. RA affects nearly 23.7 million people worldwide, with a prevalence of 0.3-1.0% of the adult population. [World Health Organization. The global burden of disease: 2004 update. Geneva: WHO Press, 2008]. As rheumatologists, we are fully aware of various disease facets- disease activity, disease disability and disease damage. Indeed, we have validated tools to measure and quantify these aspects. That disease activity is to be measured every visit is told to every rheumatologist ad infinitum. Objective assessment and response driven treatment are the key mantras in treating RA is emphasised ad nauseam. What is often overlooked and needs reiteration, reaffirmation and repetition is the societal impact of disease! RA impacts not

only the individual but also the society.

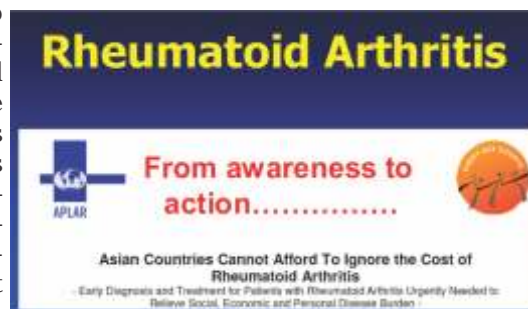
Despite advances in treatment, studies demonstrate that RA patients have not experienced the same improvement in survival as the general population, and therefore the mortality gap between RA patients and individuals without RA has



Ex-President, APLAR

widened [Gonzalez et al. Arthritis Rheum 2007, 56:3583-3587]. From a societal perspective, the loss of a younger population during productive years imposes huge costs. Work limitation and social participation restriction creep in insidiously even in people who are ostensibly doing well.

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From the Editor's Desk

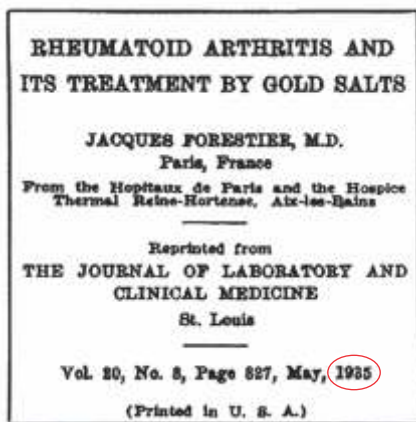


E-in-C

Dear APLAR Readers and well beyond pleasurable it has been to work for and to present this third issue of Voice of APLAR networking dispersed members in the vastness of Asia-Pacific geography and claimants to nearly two-thirds of

landmass housing nearly two-thirds of humanity. You may well perceive the need for Voice of APLAR to network our rheumatology daily endeavours. VOA provides added personal touch to humanize our communications.

The master of this fine art is Professor David Pisetsky, a prolific writer, also a Master of ACR. His thought provoking studios articles, travelogues popularized *The Rheumatologist* of ACR..... and he himself. With immense pleasure I present to you Professor David Pisetsky and his 'Reflections'..... Please do read, share and transmit his essay to your colleagues, junior or senior in Rheumatology and beyond in the world of medicine.



His vivid description of "Gold Clinic" revived my nostalgic memories : In 1980 a pretty, 30 year young lady came seeking redress of her agonizing, deformed RA joints. She was on a non-standardized Ayurvedic preparation containing gold salts ('SuvarmaBhasma'), well documented in ancient Indian literature. I injected Myo-chry-sine (the only brand by the now defunct May & Baker of the U.K.) containing sodium aurothiomaleate 50 mg weekly, co-prescribing oral chloroquine phosphate (HCQ unavailable). Within weeks gratifying therapeutic response was witnessed. Her joint pain vanished, swelling regressed, joint functional capacity enhanced. She could well manage her household chores, wake up in time to send children to school. Wonderful! Few weeks later she showed up with unmistakable dark spots (rash) on her otherwise pretty face. Although she was married, she was unhappy, so was I. Mercifully she had no other systemic side-effects: normal

BUN, serum creatinin and no proteinurea. Though disappointed she was not angry and still grateful as her RA was in remission.

I ruled out administering an antidote BAL (*British Anti Lewsite*) to eliminate deposited gold salts as there was no vital organ damage. It took some two years till her face looked like pre-treatment. But alas, developed horrendous RA joint deformities.

Another patient prescribed chloroquine returned as the pack of those tablets carried a picture of a mosquito! He gently inquired if I was making a mistake prescribing an antimalarial? He was content with my due explanation, but I still wonder why must we call chloroquine and now hydroxchloroquine an *Antimalarial*? Why not DMARD or simply '*Antirheumatic*' ? (Please do read my satirical article "Confusion or Clarity ? Nomenclature, semantics, Jargon, lingo, eponyms, etymology, and terminology in rheumatology" ... *The Rheumatologist*.2012:6 (10):10,13).

While prescribing tablet salazopyrin, nearly half of patients volunteered that they were "allergic" to "sulphas". In those yesteryears sulphonamides were commonly prescribed for infections rather any kind of "fever" provoking skin rashes.

For decades we rheumatologists were apologetic prescribing borrowed drugs (gold salts meant for treatment of TB, antimalarials deployed as antirheumatics, salazopyrine originally invented to treat RA given to Gastroenterologists for ulcerative colitis, then brought back to Rheumatology.

Some consolation: Aspirin was synthesized to alleviate pain and treat RA joints. Remember the previous Edit (Jan.2017) Von Felix Hoffman administered Aspirin to treat his father a victim of RA then John Vane proceeding to pave the way for COX-1 and COX-2 inhibiting NSAIDs winning a Nobel? These two landmark papers initiated low dose 'cytotoxics', methotrexate changed the scenario radically:



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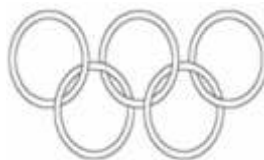
Methotrexate is the new gold standard in the treatment paradigm of RA.... I do not see anymore those horrifying deformities such as 'swan necks' ulnar deviations, peanut like swollen styloids, right angle elbows, crippling hip and knee joints, defiant deformed ankles, flattened feet, toes over one another and embarrassing corns, Do you? Stretchers and wheelchairs less utilised, ICU admissions drastically reduced, surgical referrals on the decline. Isn't this positive "societal impact" ?

When DMARD cocktails fail, and indeed they sometimes do, we can now boast of 'treat to target' molecules big or small.

How time changes and may it be so ! Rheumatology has come of age.

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Keep Moving!

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Work disability has been studied by many authors and according to conservative estimates nearly 40% of patients are unable to work within 5 years of diagnosis, and 50% within 10 years [National Institute for Health and Clinical Excellence. RA in Adults: Final Scope. 2007].

Societal Impact of RA

Mortality

1. RA kills
2. RA kills at a younger age
3. The mortality gap between RA and general population continues to persist

retirement and reduced work performance, whereas the monetary value of lost production due to the premature death of the patient is defined as a 'mortality cost'. More intangible yet the most important is the effect on quality of life.

The burden is even more in resource poor countries. The Quantitative Standard Monitoring of Patients with RA (QUEST-RA) multinational database of 8,039 patients at 86 sites in 32 countries, 16 with high gross domestic product (GDP) (>24K US dollars (USD) per capita) and 16 low-GDP countries (<11K USD) was analyzed for work and disability status at onset and over the course of RA. Work disability was seen in as many as one third of the patients. Major differences were seen in the proportion of women and men working at the onset of RA in different countries. People continue working in low-GDP countries with levels of disease activity as high as or higher than those of work-disabled people with RA in high-GDP countries.



Presenteeism or working while unwell is attracting increasing attention in RA. Rheumatologists are aware of absenteeism which has traditionally received extensive attention. Presenteeism is another way of looking at this problem. Presenteeism may account for a larger proportion of losses than absenteeism. Contribution of presenteeism on total productivity costs approximates 70% in the RA group. Costs due to presenteeism were about two to four times higher in the RA group compared with the control group [Verstappen SMM. Best Practice & Research Clin Rheumatol 2015; 29:495-511; Braakman-Jansen LMA, et al. Rheumatology 2012;51:354-361].

While caring for individuals, we must not forget the costs to the society. Early treatment can prevent disability and is cost effective Rheumatologists are uniquely placed to throw the spotlight on societal costs of RA and serve as catalysts for a greater dialogue between patients, GPs, health policy planners and governments to ensure that RA gets the priority it deserves!

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Apart from direct costs, RA imposes indirect costs. Direct costs are those for which direct payments are made and include medical and non-medical costs eg transportation, home modifications. Indirect costs are those for which no actual payments are made but for which resources are lost. These include 'morbidity costs' that represent the monetary value of lost production due to sick leave, early



In retrospect, the approach was faulty. With very few DMARDs (disease modifying anti-rheumatic drugs) in the arsenal (sulfasalazine and hydroxychloroquine were the others), we were very cautious in their use, especially as the gold salts could have menacing toxicity. For months or years, we would try NSAIDs (non-steroidal anti-inflammatory agents), switching regularly as a new one came to the market. Of course, glucocorticoids were commonly used, reluctantly and almost surreptitiously, since they worked but the price in side effects was high. The appearance of someone with severe RA was then a sad mix of a wasted body and a Cushingoid face. Impelled by X-ray evidence of joint erosion on hand films, the decision for a course of gold treatment would finally be made but by then it was too late since the damage had begun.

Many patients who attended our clinic walked with a cane or had to be pushed in a wheelchair and, of course, pain was ever present for them. I had patients who tried to make a truce with the seriousness of their disease and called their arthritis "Arthur" as if personalizing the condition, especially with an old-fashioned and not very stout name, would make it more manageable. For many patients, joint surgery was inevitable and, of course, life expectancy was diminished. While we called gold a remission-inducing or a remittive agent, in fact, true remission was quite rare. I saw more patients with serious side effects-red cell aplasia was the worst I encountered-than I saw patients whose inflammation subsided and joint swelling lessened.

At that time, some of the proposed new approaches to treat RA seemed extreme, desperate and even fanciful. Total lymphoid irradiation, plasmapheresis, and thoracic duct drainage were all in clinical trial when I started my practice and the results were not impressive. Given the severity of RA, it appeared that some drastic intervention would be needed to block disease progression, with immunosuppression of the kind used for organ transplantation likely needed to eradicate aberrant immune cell population that struck the joints. Approaches to inactivate or eliminate T cells also did not work although basic research had pinpointed T cells as a main culprit in joint inflammation.

A revolution of rheumatologic care

As it turns out, a new era in therapy began just as the prospects for advances looked the bleakest. Two innovations set the stage for modern rheumatology. The first was repurposing of a drug to treat malignancy into a DMARD for chronic use. Methotrexate (MTX) shifted the paradigm of the therapy of RA, displaying a mode of action that is still obscure. Despite much research and speculation, MTX is a mystery drug since its effects on the immune system are so subtle that they have yet to be discovered. Perhaps methotrexate causes adenosine release as suggested with Professor Bruce Cronstein. Perhaps it suppresses only

certain T cells at a particular stage in their activation pathway. Unlike other agents acting on T cells, MTX has received very little use in the setting of organ transplantation; furthermore, MTX is not usually associated with opportunistic infection. Never has a drug targeting the immune system produced such significant benefits yet have seemingly minimal effects on the number, phenotype and function of lymphoid and myeloid cells. Despite its somewhat invisible actions, MTX became the anchor of RA therapy on the basis of a combination of efficacy and safety; that position in the hierarchy of drugs remains today.

A new era in therapy

The second innovation in improving RA treatment was conceptual and philosophical. Whereas RA has long been viewed as a chronic disease, it is nevertheless amenable to **early intervention** such that aggressive therapy, often involving multiple agents including MTX, can significantly alter the disease trajectory. When I teach house staff and fellows, I like to say that RA is an acute disease with chronic consequences. That view is an oversimplification since, despite effective DMARDs that can eliminate signs and symptoms of arthritis, sub-clinical inflammation may persist for years although the intensity can wax and wane. Nevertheless, a combination of early aggressive therapy and a treat-to-target approach can induce remission in a significant number of patients, preventing joint damage, deformity and disability.

Today's drug armamentarium has been bolstered by the biologics and the new small molecules like the JAK inhibitors which are called targeted synthetic DMARDs (tsDMARDs). The array of these drugs is striking and we now have products that affect T cells, B cells and cytokines (TNF- α , IL-1, IL-6 among others); more new drugs are on the way for RA as well as psoriatic arthritis (PsA) and axial spondylitis (axSpA). In general, these drugs produce similar levels of response despite very different targets and mechanisms of action. Depending on how these drugs are used in sequence or combination, there are literally thousands of ways to treat RA. Trying to find a "best" approach to treat RA will be essentially impossible as it would require a trial design with a myriad of arms. The closest we have to such a comparative effectiveness trial is the BeST study from the Netherlands but that study only had 4 arms. The BeST study and then the TEAR trial and others have indicated that many different treatment strategies are successful as long as disease activity is kept low.

Taming rheumatoid arthritis

The revolution in RA therapy comprises early aggressive therapy and treat-to-target strategy has changed the expectations for life with RA.

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In contrast to the old picture of RA-twisted fingers, slack muscles, skin mottled with purpura, a body shrunken and fragile from osteoporosis-the appearance of patients with RA today can be essentially normal. Results of therapy are sufficiently robust in some patients to contemplate tapering or even stopping one or more of the drugs in a given regimen. The situation with PsA and axSpA is similar although there are differences in which drugs are effective. IL-17, for example, is a good target in axSpA but not RA.

For those who can get American television, I would recommend paying attention to the advertisements. In America, direct consumer advertisement is permissible and, depending on the channel and its demographics, ads for products to treat RA, inflammatory bowel disease, diabetes, opioid-induced constipation, erectile dysfunction and neuropathy are interspersed with ads for RAM trucks, Hardee's hamburgers and a sunny weekend in the Bahamas. I have even seen ads for checkpoint inhibitors and pegfilgrastim. The ads depicting patients with RA show healthy people-usually women-who move sprightly and work, dance and swim. Ads, of course, do not want to show anyone who looks sick but the appearance of patients in the ads for inflammatory conditions like RA is not too far from reality. Patients with RA today can clearly do much better now than ever before and many can lead essentially normal lives.

GDP is a new prognostic disease marker

While the availability of a large array of effective and, fortunately, relatively safe drugs are an enormous advance, there are significant challenges in how to advance treatment in a way that helps people throughout the world. At present, one of the strongest correlates of disease activity in a measure like the DAS (disease activity score) is the gross domestic product (GDP) per capita. The greater the wealth, the lower the DAS and vice versa. The levels of disease activity in wealthier countries are far lower than those in poorer countries even in the same region of the world like Europe. One informative study demonstrated that the average DAS28 value in the Netherlands is 3.1 while in Kosovo, it is 6. In the United States, socioeconomic status and level of education are also strong correlates of outcome. While I did not find data for the Asian Pacific region, I would suspect that this is the case as well.

At present, personalized or precision medicine is a popular undertaking, with large "big data" studies sifting through billions of pieces of data from genetics or genomics. The goal is to find tell-tale "omics" signals to create biomarkers to distinguish disease phenotypes and match better therapy to underlying pathogenesis. This approach has been important in oncology where already companion diagnostic or "theranostic" markers based on driver mutations help to determine therapy. In RA, endophenotypes have not yet been consistently identified beyond seropositive and seronegative patterns. On the other hand, current data indicate

that vast improvements in outcome are possible by improving access to care. Access is based on availability, affordability and acceptability and reflects insurance and reimbursement systems, regulations and the number of well-trained subspecialists. Indeed, in the United States, the zip code (the mailing code for where people live) remains a valuable biomarker since outcome is associated with the economic status of any neighborhood.

Current data indicate that vast improvements in outcomes are possible by improving access to care.

One of the biggest challenges in the therapy of inflammatory arthritis at present is economic and the distribution of therapies whose utilization carries major costs. The therapy of RA as well as PsA and axSpA can be very expensive and well beyond the means of many people and many countries. Help is perhaps on the way in terms of biosimilars although the cost savings will depend upon competition in the marketplace as well as the extent to which governmental and other health agencies use their power to negotiate lower prices. Norway has provided a striking example for how the costs of therapy can be reduced by putting a class of medication (i.e., TNF blockers) on bid. I am not sure how many other health systems will take such a bold stance. The mounting costs of RA therapy do not occur in isolation, however, since the costs of all medical treatment is constantly increasing especially as new drugs- whether antibiotics or anti-coagulants-enter clinical care. Among specialties, the cost of new drugs for oncology will likely be especially high since a setting of life and death can alter any calculus on the value of care and consideration of costs and benefits.

Time for a change: the physician as advocate, politician and partisan

If improvement in the treatment of RA can occur throughout the world, the role of the physician may have to change. Physicians may have to enter the public arena in a more visible way. As key stakeholders, they have to be advocates and maybe even partisans. In general, physicians do not engage in politics. In the US Congress, there are **only 14 physicians out of 535 senators** and representatives whereas somewhat less than 40% of all members of Congress are lawyers. Given the large impact of medicine on the economy, greater participation of those knowledgeable about the delivery of health care in the enactment of law seems important. In the United States, in a popular phrase, the need is urgent in view of efforts to reconfigure our insurance system.

The responsibility of the physician is always to the individual patient- the 30 year old woman with RA who wants to conceive a child but has joints still aflame, the 60 year old man who has been disabled by 20 years of synovitis but still wants to work- but perhaps it is time to expand the scope of responsibility to encompass not just the patient but the population in the traditional realm of public health.

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Case Report

ReA or EDS ??

Reactive arthritis or not - Yue Yang

About half a year ago, a 16-year old female patient was transferred to my outpatient clinic for evaluation of pain and swelling in her left knee of 2 months' duration. Her medical history was significant for diarrhea and fever in the previous 2.5 months after eating unclean food. She had been hospitalized in a local hospital and managed with broad-spectrum antibiotics, since when her diarrhea had stopped and her temperature decreased. However, the patient developed pain and swelling in her left knee and dactylitis of the right middle toe. Nonsteroidal anti-inflammatory drugs (NSAIDs) were administered. Dactylitis had been relieved afterwards. When the past medical history was gathered, a finding caught my attention. The young lady denied no prior history of trauma. However, she mentioned that she had experienced recurrent arthralgia since childhood. Physical examination showed tenderness and swelling of the left knee. A subcutaneous nodule of soybean size was palpated in the anterior tibial area of the left leg. Joint hypermobility and soft, velvety skin were revealed unexpectedly. Blood tests showed erythrocyte sedimentation rate (ESR) of 88 mm/h, and C-reactive protein (CRP) level of 83.15 mg/L. Human leukocyte antigen (HLA)-B27, anti-citrullinated proteins antibody (ACPA), antinuclear antibody (ANA), rheumatoid factor and antistreptolysin O titers were normal.

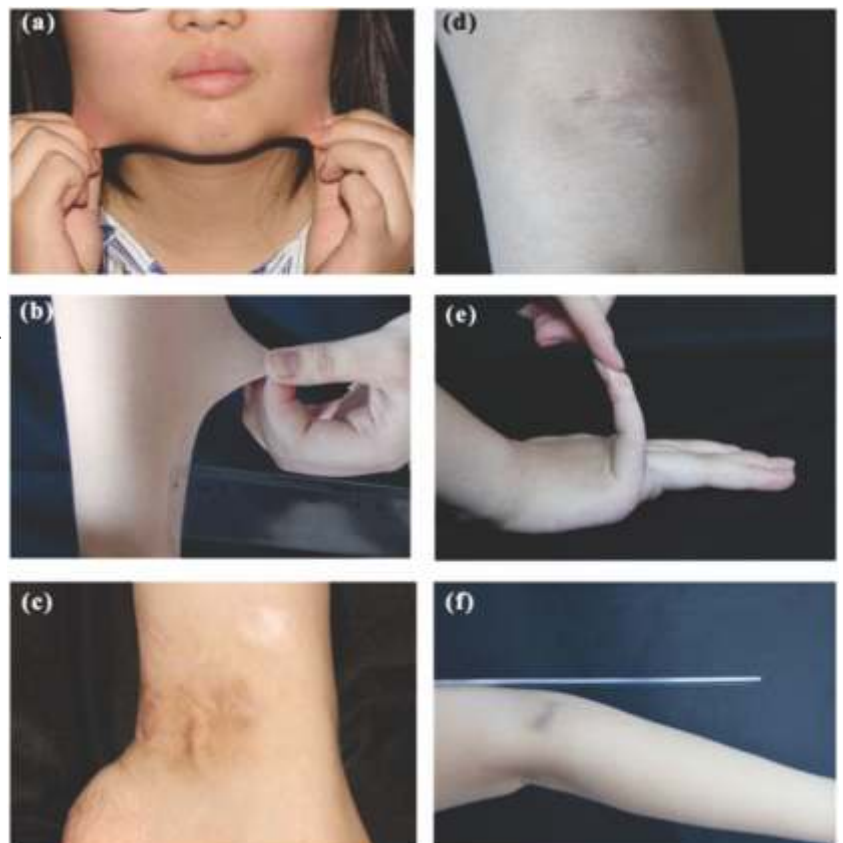
Based on findings above, a diagnosis of "reactive arthritis (ReA)" was settled. However, I kept feeling like something was missing, like a missing piece of a puzzle... Could ReA explain every complaint of the patient? How about her recurrent arthralgia since childhood, the subcutaneous nodule, and her soft velvety skin? So, when the mother of the patient said her husband had similar velvety skin, it deepened my suspicion. A skin biopsy was performed from the lower limb of the patient, which showed reduced collagen fibrils compared to the normal dermis (Fig. 1). A diagnosis flashed in my head: Ehlers-Danlos syndrome (EDS)! Further contrapuntal physical examination revealed marked skin hyperextensibility of the face and forearm; multiple scars with different types, like atrophic with a "cigarette paper" appearance, atrophic and hypertrophic, on the extremities; hypermobility of the little fingers and elbows: passive dorsiflexion of the little fingers beyond 90°, hyperextension of the elbows beyond 10° (Fig.2). The patient's genomic DNA was extracted from blood and was analyzed by the whole exome sequencing approach. It revealed a heterozygous nonsense mutation in exon 2 (NM_000093. 4: c. 265C>T; p. Gln89*) of the COL5A1 gene, not previously described in the literature, confirming the clinical suspicion. Subsequently the specific point mutation detection was performed in the proband's sister, parents and

grandmother. A similar point mutation was detected in the proband's father (Fig.3b). Classic EDS (cEDS) was diagnosed. It was a load off my mind to finally find the missing piece of the puzzle. The patient was diagnosed as cEDS and ReA.

cEDS is a rare autosomal dominant connective tissue disorder with a prevalence of around 1 in 20000. cEDS is primarily characterized by skin hyper-extensibility, widened atrophic scarring and joint hypermobility. COL5A1 and COL5A2, which encode the $\alpha 1$ and the $\alpha 2$ -chain of type V collagen respectively, when defect are considered responsible for cEDS. The most recent update of the LOVD Ehlers-Danlos Syndrome Variant Database lists 244 different mutations that affect type V collagen. Specifically, 192 distinct COL5A1 (approximately 79%) and 52 COL5A2 mutations are described (<http://www.le.ac.uk/genetics/collagen/> /October 2016). Here we found a novel nonsense mutation in exon 2 (NM_000093. 4: c. 265C>T; p. Gln89*) of the COL5A1 gene occurring in multiple members of a Chinese family.

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Fig 1. Clinical findings of the proband. (a-b) Marked skin hyperextensibility on the face and forearm; (c-d) Different scar types, atrophic with a "cigarette paper" appearance, atrophic and hypertrophic; (e-f) Hypermobility of the little finger and the elbow: passive dorsiflexion of the little fingers beyond 90°, hyperextension of the elbows beyond 10°.



...continued from page 5 - Reflections on Modern Rheumatology - by David Pisetsky

Precision or personalized medicine is a laudable goal but, if the personal traits associated with poor outcome relate to access to care, identifying genomic or genetic signatures will not have much impact if the correct drugs are either unavailable or unaffordable.

Given the large impact of medicine on the economy, greater participation of those knowledgeable about the delivery of health care in the enactment of law seems important.

The advent of targeted therapy has been an incredible advance for rheumatology and outcomes are better today than at any time in the past. Now may be the time to move the target from the person to the population to ensure that everyone - no matter wealth or social standing - has a chance to benefit from the revolution in arthritis treatment that has been so brilliantly created.

Suggested Reading (1-5)

1. Malaviya AN, Gogia SB. Treatment of rheumatoid arthritis (RA) in India-how and by whom: results from a speciality clinic-use of low-dose methotrexate (MTX) was inexplicably suboptimal. *Clin Rheumatol.* 2016;35(9):2163-73.
2. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis.* 2014;73(1):198-206.
3. Putrik P, Ramiro S, Kvien TK, Sokka T, Uhlig T, Boonen A. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? *Ann Rheum Dis.* 2014;73(11):2010-21.
4. Sokka T, Kautiainen H, Pincus T, Toloza S, da Rocha Castelar Pinheiro G, Lazovskis J, et al. Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. *Ann Rheum Dis.* 2009;68(11):1666-72.
5. Zhao S, Chen Y, Chen H. Sociodemographic factors associated with functional disability in outpatients with rheumatoid arthritis in Southwest China. *Clin Rheumatol.* 2015;34(5):845-51.

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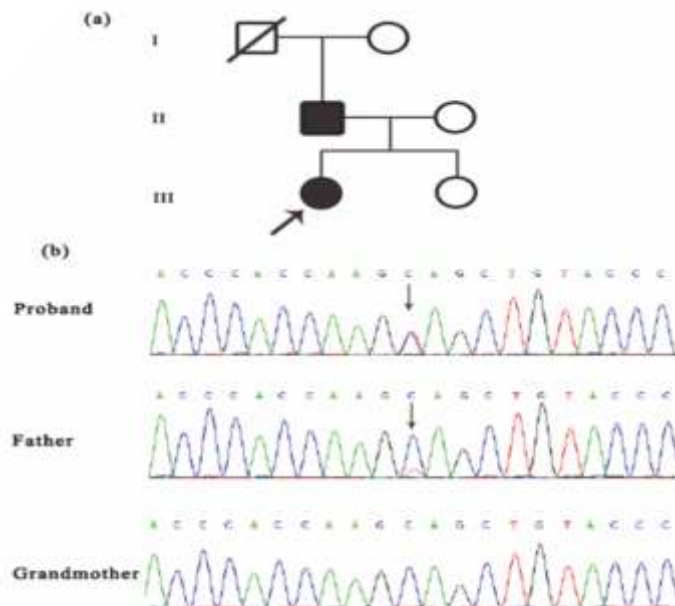
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...continued from page 6 - ReA or EDS ? - Yue Yang

The case reminds me the reason why I wanted to be a physician at first. To find a diagnosis, sometimes, is like to catch a culprit. After we "round up the usual suspects," we rule each of them out as best we can, and then focus on what is left. As Sherlock Holmes said, "How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?". Once not a single clue is missing, you have the right answer.

Fig 2. (a) Pedigree of family with cEDS. Filled symbols represent affected individuals. (b) Familial genetic study of mutation in exon 2 (NM_000093.4: c. 265C>T; p. Gln89*) of COL5A1 is found in the proband and her father, compared to the normal sequence of the grandmother.

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Snippet ... True personal anecdote

In 1990s the Editor of an Indian medical textbook insisted I write on Ehlers-Danlos Syndrome (EDS). I did so reluctantly as I had probably not seen a patient of rare EDS since years.

A month later joining a Grand Round at QE2 Hospital in Perth, a patient presented with Hypermobility Syndrome with rubber like elastic skin over forearms. As Residents wondered, I shot the spot diagnosis: EDS.

That evening Professor Owens, the then President of Australian Rheumatism Association took me to dinner.

----- Prakash Pispati

Real pain in the neck !!



E-in-C



The elusive target for Biological Therapy?? Valuable lessons - Shankar Subramanian

Biological agents or Biologics, therapeutic agents with biologic properties, have revolutionized the treatment of immunological diseases in the last decade or so. These agents, including monoclonal antibodies and soluble cytokine receptors, have demonstrated profound efficacy with reduced toxicity in various autoimmune disorders. Their impact of these innovations have maximally benefitted Rheumatology, Dermatology and Neurology while autoimmune kidney diseases have gained much. Biologic after biologic have failed in Lupus Nephritis, one of the commonest autoimmune renal disease. Rituximab did appear promising in various observational studies but the Lunar study was a clear setback. It is hoped that the Rituxilup trial, that compares Rituximab with MMF might provide a definitive answer in 2019. The story for various other autoimmune renal diseases is quite similar. While almost 8-10 different biologics have been found to be effective in management of rheumatoid arthritis, as of today, there are just 3 agents that are FDA approved, that have shown some promise in renal autoimmune diseases. (Table 1). The list of fallen heroes is almost 5 times higher. **This discrepancy is perplexing.** Is the difference explained by some unique biological difference in the kidneys or are there certain conceptual hurdles?

The International Society of Nephrology organized a global Nexus meeting on the topic of “**Translational Immunology in Nephrology**” in Berlin, Germany, in April 2016 to precisely attempt to answer this query. During this meeting, experts and participants from basic science, clinical science, pharmaceutical industry, and regulatory bodies defined problems and discussed potential solutions.

The meeting identified many conceptual hurdles. Prominent among them were a need to reclassify renal syndromes based on their pathogenetic pathways rather than their histology. The probability of identifying effective targeted therapy increases if one focuses on pathogenesis rather than the histology which is often a potpourri of diverse diseases. Almost all renal autoimmune diseases belong to the realm of rare diseases. The incidence varies from 0.25-2.5/100000 population for different illnesses. Hence making consortiums are a necessity to conduct trials to achieve adequate sample size and get meaningful results. Single centers would find it extremely difficult to muster numbers for clinical trials. There is a signifi-

cant discrepancy between animal renal models and human trials. For eg. The animal renal models are assessed by sacrificing the animals and assessing renal histology while the human trials usually look at proteinuria, serum creatinine levels or other biomarkers as primary outcome measures. Also, almost all animal models compare the drugs one on one while the human trials almost always have an add on model. For eg, though rituximab was promising in animal models of lupus nephritis when tested in comparison with other immunosuppressives, in the Lunar trial it was given to patients after optimum steroid dose and immunosuppression with mycophenolatemofetil. Another key aspect is the lack of biomarkers of intrarenal inflammation, injury or a biomarker to measure nephron number. Besides the hurdles mentioned above, the conference identified many more challenges in renal autoimmunity.

The wisdom of **learning from failure** is incontrovertible. Yet organizations that do it well are extraordinarily rare. Besides the academic interest of knowing why renal autoimmune diseases have a poor response, what is truly remarkable is the approach taken at the Berlin conference. A meeting of experts ranging from basic scientists to practicing nephrologists bring their unique perspectives to the brainstorming. Research gaps get identified when viewed from a different lens. Newer directions to explore the same problem emerge.

Only time will tell whether it is the unique physiology of kidney or is it the hidden conceptual hurdles that were responsible for this discrepancy in response to biologics. Whatever the answer might be, an important lesson learnt is **to share ideas across** various disciplines as was done at the Berlin conference.

Recommended Reading

1. Anders HJ, Jayne DR, Rovin BH. Hurdles to the introduction of new therapies for immune-mediated kidney diseases. *Nat Rev Nephrol.* 2016 Apr;12(4):205-16.
2. Holdsworth SR, Gan PY, Kitching AR. Biologics for the treatment of autoimmune renal diseases. *Nat Rev Nephrol.* 2016 Apr;12(4):217-31.

Gp Capt S Shankar

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Associate Editor, VoA

Past Editor, Indian Journal of Rheumatology
(<http://www.indianjrheumatol.com/>)



Table:

Biologics approved by FDA for Renal autoimmune disorders

Sr. No	Name	Target	Disease
1	Rituximab	Anti CD 20	ANCA associated Vasculitis
2	Eculizumab	Complement Inhibitor	Atypical HUS
3	Belatacept	Selective T cell co stimulation	Transplant rejection

Rheumatology in Taiwan: APLAR Congress 2018

Taiwan, officially the Republic of China (ROC), is a country of twenty-three million inhabitants that has always been influential economically and culturally in East Asia. In 1982, Taiwan Rheumatology Association (TRA) was founded due to the increasing number of patients with rheumatic diseases and the rising demand for clinical researches. Currently, the association has more than 300 Rheumatologists who had been certificated by qualification exams to ensure core knowledge and skills for patient care. RA, AS, SLE and gout are among the most common diseases which Rheumatologists have to deal with. In 1995, Taiwan launched the National Health Insurance program with more than 99.9% coverage of Taiwan's population. Till now, more than 2,300 scientific papers have been published using this large computerized research databases. Biological and targeted synthetic disease-modifying anti-rheumatic drugs for rheumatic diseases are generally reimbursed by Taiwan National Health Insurance. We follow the NICE guideline for the reimbursement of biologic agents for RA patients. Now, more than 5000 RA and 3000 AS patients are reimbursed for biologic agents. In particular, RA was considered as a catastrophic disease. Patients are 100% totally reimbursed for their medication, including biologics. Patients don't have to pay a single penny. In 2012, risk management plan of screening and treatment of latent tuberculosis (TB) and hepatitis B



virus (HBV) infection before initiation of biologics was implemented nationwide. Following this preventive strategy, the incidences of latent TB and HBV flare has been reduced. Meanwhile, considering dose-dependent adverse effects and economic burden of biological therapy, the Taiwan Health Insurance Bureau put forward a dose reduction policy in 2013. In rheumatoid arthritis patients who achieve low disease activity after 2 years of therapy, dose-halving strategy would be considered after having tapered glucocorticoid. In 2016, TRA advocated nine study interest groups of systemic autoimmune diseases and epidemiology to coordinate collaborate researches of entire country. In 2018, the 20th Asia Pacific League of Associations for Rheumatology Congress will be held in **Kaohsiung, Taiwan** in conjunction with TRA annual congress. Kaohsiung is a harbor city with beautiful beach and delicious food. It would be a not to miss opportunity to exchange cutting-edge scientific and clinical information in the world of Rheumatology. Welcome to Taiwan and experience Formosa, the "hidden gem of Asia".

YOU ARE INVITED

RSVP:
 Yi-Ming Chen¹, Wen-Chan Tsai²
 1. Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taiwan, R.O.C.
 2. Department of Internal Medicine, Kaohsiung Medical University Hospital, Taiwan, R.O.C.

The 5th Scientific Meeting of the Asian Federation of Osteoporosis Societies 2017

Theme: *Best Practices, Future Directions.*

Date: 6th – 8th October 2017 | Venue: Hilton Kuala Lumpur, Malaysia

IMPORTANT DATE
 Registration & Abstract submission opening in **1st January 2017.**
 Abstract will be published in AFOS Journal Osteoporosis & Sacropenia.

www.afos2017malaysia.com | Email: secretariat@afos2017malaysia.com



From Professor Graham R V Hughes, London

Dear Prakash,

Many congratulations on Voice of Aplar – an outstanding piece of work. May it have a long and successful life!

Thank you also for the article on Hughes Syndrome – I found it both accurate and beautifully written. I was

honoured by your effort.

With very best regards,
Graham

Professor Graham R V Hughes MD FRCP
Head of The London Lupus Centre
London Bridge Hospital
27 Tooley Street, London SE1 2PR.



From Dr Anand Malaviya, New Delhi

Sir,

Read the post 'From the Editor's Desk' in the 2nd (January 2017) issue of the 'Voice of APLAR' with great interest. It was a nostalgic reminder "A few pundits termed NSAIDs not pain killers, but 'plain killers'" by the Editor-in-Chief Dr Prakash Pispati, a close friend. Was he quoting me? Most probably! In the '1980s I often reminded the audiences about the harms of prolonged, mostly unsupervised, use of painkillers often in the elderly. Two recent papers remind us that the debate is still 'on' [1-4] and, by-and-large, I still hold a similar viewpoint about NSAIDs/coxibs. Rofecoxib and valdecoxib scandal of 2004 and 2005 had jolted most of us rheumatologists. Besides that, our nephrologist colleagues have been taunting us for decades as 'kidney killers' and kept reminding us of the adverse effects of NSAIDs on kidney. Time and space do not permit quoting a large body of evidence of their adverse effect on cardiovascular system, renal functions and the gastrointestinal tract albeit with prolonged and unsupervised use. The papers quoted above would support this viewpoint.

No rheumatologist should ever overlook the need for pain-relief. That can be done with a careful evaluation of the cause of pain. Is the pain due to suboptimal dose of DMARDs in inflammatory arthritis with persistent synovitis and disease activity? Or, is the pain due to structural-mechanical damage? Last but not the least; is the pain due to depression and fibromyalgia? I am sure NSAIDs/coxibs would not be considered ideal for

persistent synovitis due to suboptimal DMARDs or in patients with fibromyalgia! On the other hand, mechanical-structural damage-related pains must be assessed by the occupational therapist and a surgeon if some physiatry help or a minor/major surgical intervention could relieve the pain. But, in situations where NSAIDs/coxibs give dramatic pain relief with a bonus of suppressing inflammation (e.g. axial spondyloarthritis), they remain unquestionably the first-line drugs. Fortunately, this group of patients is usually below 40-45 years of age who would tolerate NSAIDs/coxibs quite well, much better than their elderly counterparts.

The NSAID/Coxib pendulum had swung from one extreme 'they are plain killers' to the other 'they are simple benign drugs effectively relieving pain'. That is where Editor's wise words 'keeping a balance, everything in moderation' would come handy.

Anand N. Malaviya,

ACR and APLAR Master, Rheumatologist, New Delhi.

References:

1. Nurmohamed MT. Cardiovascular safety of celecoxib, naproxen and ibuprofen. *Nature Rev Rheumatol* 2017; 13:136-8.
2. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. (The PRECISION trial) *N Engl J Med* 2016; 375: 375:2519-29
3. Arthritis Research UK: <http://www.arthritisresearchuk.org/health-professionals-and-students/reports/topical-reviews/topical-reviews-spring-2010.aspx>;
4. Arfè A, Scotti L, Varas-Lorenzo C. et al. Non-steroidal Anti-inflammatory Drugs and Risk of Heart Failure in Four European Countries: Nested Case-control Study. *BMJ*. 2016;354(i4857)

Kaliningrad Immunology - Rheumatology Scientific Research Forum - by Mark Goloviznin, Moscow

As a regular participant in APLAR Congresses which I enjoy, I wish to highlight this significant event on June 27-30, 2016 in the beautiful city of Kaliningrad. Russian Federation was host to this Forum announced on APLAR web-site as the Russian Cytokines Society is already an Associate APLAR member was co-organizer of the event, also under the aegis of:

- Emanuel Kant Baltic Federal University
- The Ministry of Health of the Kaliningrad region
- The Institute of Immunology and Physiology of Russian Academy of Sciences.
- The Russian Scientific Society of Immunologists

- Russian Cytokines Society.

In four exciting days delegates could enjoy the rich scientific programme, inspiring discussions between leading Russian and visiting scientists with the backdrop of rich cultural programme in ancient city of Königsberg on the Baltic coast basking in midnight sun and "white nights" when street lights are switched off!

Program had a rich fare: 12 symposia, 2 master classes, seminars and round tables, eg:

"Autoimmunity", "Molecular and cellular mechanisms of immune regulation", "Immunology of reproduction",

...continued on page 11





5TH WORLD CONGRESS
on Controversies, Debates & Consensus
in **Bone, Muscle & Joint Diseases**

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Monday, April 3, 2017

Early fee deadline

Wednesday, June 28, 2017

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(...continued from page 10)

"Immunopharmacology and immunotherapy", "Infectious immunology", "Actual problems of immunophysiology", "Cell technologies applied to immunological research", "Primary immunodeficiencies", "Translational biomedicine: modern methods of interdisciplinary research", "Cell technology in the diagnostics and treatment", "Biological and biotechnological bases of tissue engineering". The seminar of «Beckman Coulter» «Multicolor cytometry - Find your subset». "The Master Class of «Beckman Coulter» devoted to flow cytometry, Theround table "Legal regulation of the development, deployment and commercialization of innovative biomedical products".

Enlightening Plenary Lectures by:

Professor V.A. Kozlov: "Immunological doctrine of major diseases of contemporary human being" (Novosibirsk)

"Immunopatofiziologiya inflammation" (Ekaterinburg)

Professor A.S. Simbirtsev: "Cytokine and Anticytokinetherapy" (St. Petersburg)

Professor AP Prodeus: "Practical approaches to the diagnosis of immunodeficiency conditions in children and adults" (Moscow)

Dr Sci KV Shmagel: "The immune system activation and inflammation in HIV / HCV co-infection" (Perm)

Professor BV Pinegin: "The endogenous activators of innate immunity" (Moscow)

At symposium devoted to "Autoimmunity problems" report of leading Indian rheumatologist, past President of APLAR Prof PrakashPispati (Mumbai, India) "Microbiome - autoimmunity interface" was presented and produced great interest.

540 scientists – rheumatology delegates from all over Russia and invited foreign faculty were regaled with cultural dances at the finale.

Professor Mark Goloviznin, Moscow

Associate Professor, Moscow State University of Medicine and Dentistry



Prof. Mark with Prof. Chereshev

I had the honour to address the Forum and was asked to raise a toast at the annual dinner whetted by authentic Stolichnaya and Caviar:

"HAIL RHEUMANOLOGY ..., SPACIBA"
Rheumatology + Immunology Thank you

... Prakash Pispati



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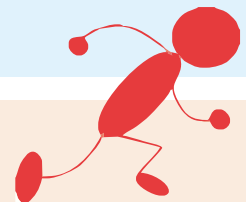
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