



Mosaic of Autoimmunity
Abdulla Watad
Yehuda Shoenfeld

Page 1, 2, 3

DEBATE
DMARDs vs Biologicals
Anand Malaviya
Shankar Subramanian

Page 5,6,7,8

Story retold :
Hughes Syndrome
Prakash Pispati

Page 9, 10

VoA
Editorial

Page 4



Prof. Kevin Pile
President, APLAR... Australia

Welcome to the first edition of the "Voice of APLAR" and whilst it should not be confused with 'The Voice' I am confident it will be just as popular, entertaining and on occasions controversial. This launch edition coincides with and mirrors the 2016 APLAR Congress in its acknowledgment of the past of rheumatology, updating it, and making it relevant for the future in a vibrant and interactive way.

My personal thanks and acknowledgment go to the VOA's Editor-in-Chief and APLAR Past President, Dr Prakash Pispati, who has persistently emphasised the need for APLAR to communicate and enhance the relationships amongst the rheumatologists of Asia-Pacific. He has put his labour to the task, so please reward him with your readership and contributions.



Prof. Kazuhiko Yamamoto
APLAR, President Elect ... Japan

I am really expecting that "Voice of APLAR" will deliver a variety of communications among rheumatologists within APLAR and all over the world.

18th APLAR, CRA Joint Congress Sept 26-29, 2016, Shanghai.

Prof. Xiaofeng Zeng,
Chair, President,
Chinese Rheumatology Association.



This Congress provides a wonderful platform for leading rheumatologists to present their cutting-edge research work and discuss about the hot-tops of rheumatology, to meet and network for about 2000 delegates from the world over. (... continued on page 3)

Proudly presents
Voice Of APLAR heumatology

Editor-in-Chief

Dr Prakash Pispati, Mumbai, India.
Past President APLAR, IRA
Master, Hon. Member



Novel Factors Which Orchestrate the Mosaic of Autoimmunity - 2016

-Abdulla Watad | Shoenfeld Yehuda

• Why do we develop an autoimmune disease?

The term of "why she or he" develops an autoimmune disease is behind all the pathogenesis of these kind of diseases. Why the autoimmune diseases are more common in females? Why in a certain family some develop the disease and not the whole family? The explanation and the answers for this enigma is found in a book written in 1988 by our group and titled "The Mosaic of Autoimmunity". At that time, the book summarized all the factors that may contribute in the development of a specific autoimmune disease in an individual. The factors were classified into three categories: Genetic factors, Immune system dysregulation (complement system disorders, T cells dysfunction, etc.), Hormonal factors (estrogen, progesterone, prolactin, vitamin D), and Environmental factors (Fig 1).

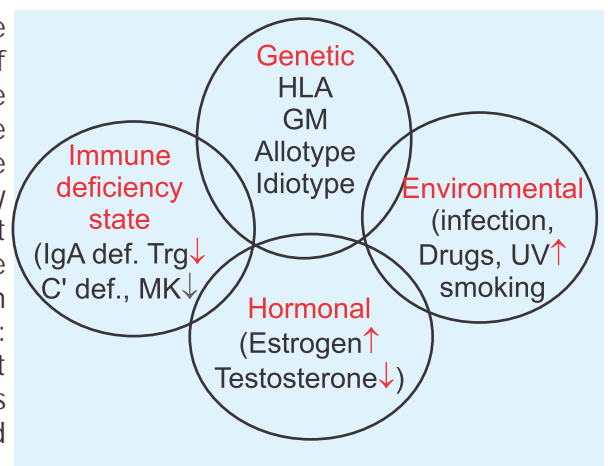


Figure 1 - The Mosaic of Autoimmunity 1989

continued on page 2



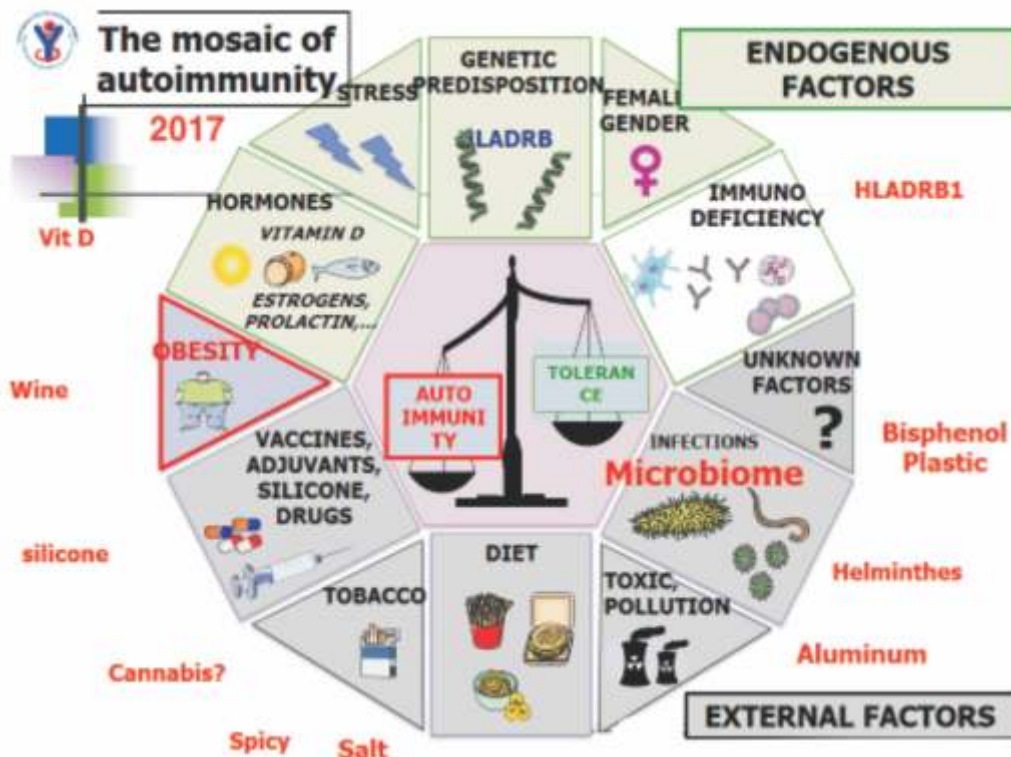


Figure 2

There is a very wide spectrum of environmental factors including, infections (viral and bacterial), UV exposure, stress, Etc. Interestingly, to have an autoimmune disease there is a need for the coexistence of these four factors. The diversity of these factors may explain the presence of diverse autoimmune diseases, why in a certain family the mother has SLE, the son developed diabetes mellitus type I and the daughter developed pemphigus vulgaris. Additionally, this complex explains why an individual may have more than one autoimmune disease. Twenty-five years' after the printing of the titled book "The Mosaic of Autoimmunity", other additional important environmental factors were described. These include dietary factors (salt, spicy food protective factor), smoking, and obesity (Fig 2).

● Who is at risk to have an autoimmune disease.?

The genetic predisposition plays a pivotal role in all autoimmune diseases. Indeed, these individuals possess a very active and effective immune system. In one hand, being immunocompetent means being able to defend oneself against potentially damaging microbes and parasites. The other hand, too much immune activity may lead to non-desired immune reactions towards the self-antigens and therefore to cause injury to the tissues and organs. Now a days, we have the possibility to identify individuals with genetic predisposition to autoimmune diseases by the recognition of specific haplotypes of the

HLA system. Divers haplotypes were described to be linked to the development of autoimmune diseases including (HLA-DRB1), (HLA-A1*BA*DR3), etc. Carriers of the latest haplotype possess 10 times more risk to develop an autoimmune disease in comparison to normal controls. Females are also at higher risk, they have a better and more effective immune system. Females respond more effectively to vaccines in comparison to males. Lymphocytes of females present estrogen receptors, which can stimulate the immune reactions through the production of BLYS (B lymphocyte stimulating factor).

This interesting finding may explain why autoimmune diseases usually induced in the fertile period, the effect of IVF (in vitro fertilization) or the intake of contraceptives on the development or the course of autoimmune diseases. Moreover, pregnancy and post-partum are linked to autoimmune diseases, characterized by immune-endocrine changes occur in order to achieve immunosuppression and tolerance by the immune system to paternal and fetal antigens. These conditions may exacerbate some autoimmune disease and ameliorate others. The impact of estrogens on the immune system is momentous. Not only natural hormones, but also endocrine disruptors, such as environmental estrogens, act in conjunction with other factors to override immune tolerance to self-antigens.

Of all, most probably the most important environmental factor is infection by a microbial agent. There are five main mechanisms by which such an infection can lead to an autoimmune disease. These mechanisms are as follows: molecular mimicry, "epitope spreading", polyclonal activation, and viral and bacterial super-antigens that possess the ability to bind to the variable domain of the T cell receptor beta chain. Environmental factors entail an immune adjuvant activity such as infectious agents, silicone, aluminum, salt and others were associated with defined and non-defined immune mediated diseases, both in animal models and in humans. These adjuvants may affect diverse components of the immune system through the innate immune response by the activation of TLR-4/9, the production of uric acid and others. Adjuvants can be found in most vaccines, and therefore genetically predisposed individuals may develop an autoimmune disease due to vaccination. In contrary to what was thought, silicone is not an inert material. A rupture of silicone implants leads to the leak of silicone particles, which can stimulate the immune system and to develop an autoimmune disease. These findings were behind the description of the ASIA syndrome "autoimmune/inflammatory syndrome induced by adjuvants" (3). In according to the mentioned above, together with the better understanding of the pathogenesis of the autoimmune diseases led not only to the development of potential therapeutic aspects but also to the evolution of the preventive therapeutic strategies. Prevention of autoimmune diseases can be verified through the identification of individuals at high risk, and in the future, a genetic chip testing might be available to recognize specific haplotypes linked to autoimmune diseases. For now, the past history still a key role in the identification of high risk groups. In these individuals, there is need to think

over very carefully and to consider the risk in exposing them to diverse adjuvants such as vaccines, silicon implants etc. Other preventive strategies include vitamin D supplementation, avoiding exaggerated UV exposure, cessation of smoking, weight loss, spicy food and curcumin.

● Conclusion

Recent advances in the understanding of the pathogenesis of autoimmune diseases have resulted not only in the use of biological agents that are target-oriented therapy, but also in the development of diverse preventive strategies of these diseases.

References: 1. Shoenfeld Y, Zandman-Goddard G, Stojanovich L, Cutolo M, Amital H, Levy Y, et al. The mosaic of autoimmunity: Hormonal and environmental factors involved in autoimmune diseases - 2008. *Isr Med Assoc J.* 2008; 10(1):812.

2. Shoenfeld Y, Blank M, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, et al. The mosaic of autoimmunity: Prediction, autoantibodies, and therapy in autoimmune diseases - 2008. *Isr Med Assoc J.* 2008; 10(1):139.

3. Colafrancesco S, Perricone C, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants and Sjogrens syndrome. *Isr Med Assoc J.* 2016;18(3-4):1503.

^{1,2}Abdulla Watad MD, ³Shoenfeld Yehuda MD, FRCP, MaACR

¹Department of Medicine 'B', ²Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer Israel, ³Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Keywords: autoimmunity, mosaic of autoimmunity, environment, obesity, spicy food, curcumin, smoking, pregnancy, vaccines.

Address for correspondence:

Prof. Shoenfeld Yehuda, MD, FRCP, MaACR
Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center (Affiliated to Tel-Aviv University)
Tel-Hashomer 5265601, Israel.

Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel.

Tel: +972-3-5352855 | Fax: +972-52-6669020.

E-mail: shoenfel@post.tau.ac.il

(... continued from page 1)

● Welcome you cordially to Shanghai, China!

ACR and EULAR are also invited to join the congress and the potential of building future collaborations with APLAR will be extensively explored and discussed. The meeting between APLAR and ACR will be hold during the pre-congress session and EULAR will be met during the parallel session.

I must mention that Shanghai is a beautiful city with many unique features. It is the prototype of integration of wonderful traditional Chinese culture and modern civilization. If Yuyuan and Huangpu River are the representatives of old Shanghai, then Mingzhu Tower is the marker of rapid development of modern Shanghai. As this APLAR congress will lead you to surfing in the ocean of the advances knowledge of rheumatology, it also enables you understand the rich and colorful Chinese culture in depth at the same time... **Prof. Xiaofeng Zeng.**





Inaugural Editorial Welcome



E-in-C

voice of apl ar, **VOA** is actually yours, so raise your voice because APLAR is yours. Yes, there are journals and journals; APLAR is proud of the International Journal of Rheumatic Diseases (IJRD) where research papers, detailed articles on specific topics appear. **VOA** complements, differently.

The Inaugural issue is adorned with greetings from APLAR President Kevin Pile, President-Elect Kazuhiko Yamamoto, National Societies who responded in good time and sister organizations ACR, EULAR. Great going, thanks to them, Executive Committee members and Ms. Coralie Deguerville our APLAR Manager, Singapore.

VOA is for relaxed easy reading on Rheumatology themes in line with the way we work all day long toiling, feeling, touching rheumatic patients at our hospitals and clinics offering solace to our patients.

Our science is 'bread and butter' for our body, mind and soul. It is dynamic, exciting, let's not forget it's even loaded with scientific adventures, imaginative ideas, positive emotions. Let us capture and express these fine emotions. APLAR is 29 countries strong, more to come; so diverse, so spread out (more than half of world's landmass and people). We need to network regularly in a friendly way. That's why, **VOA**.

A modest quarterly e-Bulletin for a start, let it be your identity. Feel free to pick up your pen, rather fiddle your "mouse" and write freely on whatever you feel like. The Editorial team under formation will be receptive, with the usual 'cuts and fits'. Your active participation, your forgiveness for our imperfections, your blessings is all we ask.

VOA with one voice *Viva APLAR!*

From the Editor's Desk

The Debate presented is a new dimension. The erudite Professor Anand Malaviya (New Delhi) is taking on **Biologicals** advocating conventional **DMARDs** are as good in treating RA.

Are they ? The brilliant Group Capt. Dr. Shankar Subramanian (Bangalore) presents counter-arguments logically. What do you think ? Have biologicals reached their plateau? Are we justified in prescribing such expensive products in RA patients in whom DMARDs seem equally as good as of recent studies? Is this now a case to delineate rather than compare Biologicals with DMARDs in the same breath? Are these competitive or complementary? Are we optimizing biologicals for short induction therapy, and cheaper DMARDs to take over to maintain remission ? We should, I believe.

And what of dramatic impact of Biologicals on quality of lives of crippling patients of RA, not to speak of ankylosing spondylitis and those embarrassing manifestations of psoriasis ... often sparing expensive joint replacements ? If only biologicals are used

before and not after deformities have set in. Haven't some Biologicals salvaged many patients of deadly vasculitis ?

After about 10 years of experience with Biologicals we rheumatologists seem maturing to optimize the virtues of costly Biologicals making them cost-effective... cutting short rather boring "lifelong" DMARDs. Aren't Biosimilars an accepted reality ? I may be wrong, probably right. Indeed this thought provoking debate presented should evoke your views, your experiences, **your VOTE**

For the Proposition

For the Opposition

Please tick and email on

prakashpispati@vsnl.net

prakashpispati@gmail.com

VOA welcomes your experiences, your articles, your cases, your anecdotes ... meant for meaningful yet easy, light, humane Rheumatology reading.

Good Luck... God Speed... Cheers !





DEBATE



WHY this irrational rush towards Biologicals ?

Proponent : Anand Malaviya*

● The patient and her family

Imagine the facial expression of a man, a Primary School Teacher with a salary of Rs. 16,500 per month, who has just been told by the doctor that his wife now requires a medicine that would cost Rs. 5700/week X many weeks ! Bemused, amused ('you must be joking!'), shocked, perplexed or plain confused? She had been earlier prescribed methotrexate (MTX) 7.5 mg/week along with intramuscular injections of 80 mg 'Depomedrol' every 7-10 days. At the end of 6 weeks, she still had improved hardly. Therefore, the MTX dose was increased to 10 mg/week while 'Depomedrol' IM injections continued. She felt slightly better but still, was unable to carry out the daily chores. At this stage, the physician advised the expensive medicine (etanercept biosimilar, a relatively cheap biological in India).

● Was the Medical College Physician right in his opinion ?

That's right, as per the American College of Rheumatology (ACR) 2015 guideline recommendations. However, if one can sift through the PICO questions and the GRADE evidence of this (probably the best written) evidence-based scientific document till to date, one may have to change the opinion. Look at table 1 'Key provisos and principles' point 2. It says 'cost is a consideration in these recommendations'. Also, under the heading 'How to interpret the recommendations' point 1, it emphasises '.....but some (patients) may not want to follow the advice. Because of this, always warrant a shared decision-making approach'.

● Was the MTX treatment optimised before suggesting the biological ?

The author has recently published that among 316 RA patients presenting to his clinic 44 % had never been prescribed MTX. Of the other 56% patients, 29% were never prescribed MTX at the dose > 12.5 mg/week ! This is despite several authoritative publications on MTX dose and dosing for optimising the efficacy of the drug. Starting dose of MTX of 15 mg/week (if no contraindications) preferably parenterally up-front , rapidly escalating the dose to 25 or even 30 mg/week (if required) is the present-day method of using MTX in the treatment of inflammatory rheumatic diseases. Knowledge deficit cannot and should not be an excuse to promote biologicals, which most Indians cannot afford.

Even among patients having "inadequate treatment response", ACR guideline recommend an effective alternative i.e. cost-effective combinations of csDMARDs. Several studies have clearly established that this form of treatment is cost-effective.



● Efficacy of csDMARD combinations in the treatment of RA

I am sure most elder rheumatologists around the world remember a paper by the father of the modern-day DMARD-combination therapy for RA - the famous American rheumatologist Daniel J. McCarty and his landmark 1990 paper entitled 'Suppress rheumatoid arthritis early and leave the pyramid for the Egyptians' !. The 2 seminal papers by O'Dell, Tug well et al and colleagues in 1996 needs special mention as they demonstrated that the combination of MTX, HCQ and SSZ was superior to monotherapy or double therapy with these drugs. For the sake of brevity, the reader is referred to the paper by O'Dell for several other effective DMARD combinations including the combination of MTX with leflunomide by Kremer et al. The other seminal papers demonstrating high efficacy of combination DMARDs that must be mentioned include the FinRACo-trial (first published in 2002) by the Finnish rheumatologists , COBRA , CAMERA , CIMESTRA, CARDERA , CARDERA follow-up TReACH . It must be mentioned that one of the most popular DMARD combination remains that of MTX+HCQ .

● csDMARD combinations versus bDMARDs+MTX - head-to-head trials

Let us go straight to the point namely, are csDMARD-combos less efficient in RA than bDMARDs? What do the studies on the head-to-head comparison of csDMARD combos with the bDMARDs show? TEAR trial and its follow-up, as well as SWEFOT trial and its follow-up , show that at the end of 2 years there was no difference in the disease outcome between those on csDMARD combos versus those on bDMARDs. Moreover, the bonus was a better cardiovascular risk protection with csDMARD combos. Also, no difference was discernible between infliximab+MTX versus triple-DMARD treatment regimens in the level of work loss days . However, of interest for countries (... continued on Page 6)

in our region of the world would be the fact that csDMARD combos are highly cost-effective as already mentioned above. In this regards recent reports from the USA are rather disturbing; rheumatologists are prescribing bDMARDs without optimising csDMARDs.

● Most cost-effective treatment for RA - evidence based

Finally, as far as the strength of the evidence is concerned one of the most respected and authoritative publication is the 'Cochrane Review'. An abridged Cochrane systematic review and network meta-analysis on the issue of MTX monotherapy and MTX combination therapy with csDMARDs and bDMARDs for RA has been published recently. This Cochrane network meta-analysis included 158 trials with more than 37 000 patients. It says, and I quote: "Triple therapy" (methotrexate plus sulfasalazine plus hydroxychloroquine) was superior to methotrexate alone and not statistically different from methotrexate plus any biologic DMARD or tofacitinib for controlling disease activity, either as initial therapy or after an inadequate response to methotrexate. Given the low cost of triple therapy compared to biologic DMARDs and tofacitinib, these findings support a therapeutic trial of triple therapy as initial treatment or after an

inadequate response to methotrexate'. Based on this evidence the treatment paradigm for RA should shift in favour of cost-effective methotrexate combination therapy with traditional DMARDs before embarking upon the more expensive treatment with bDMARDs.

● Conclusion

Based on the irrefutable evidence I feel that the resource constrained countries in the world would be better off following the cheaper but equally effective option of csDMARD optimisation and csDMARD combos.

*Author:

Professor Anand N. Malaviya, MD, FRCP (Hon. Lond), Master-ACR, FACP, FICP, FAMS, FNASC; (Rtd. Chairman, Dept. of Medicine, and Chief of Clinical Immunology & Rheumatology Services, All-India Institute of Medical Sciences; (Presently): Head of the Department of Rheumatology, ISIC Superspeciality Hospital, Vasant Kunj) and Consultant Rheumatologist, 'A&R' Clinic for Arthritis & Rheumatism, Vasant Kunj, New Delhi, INDIA - 110070.

Email: anand_malaviya@yahoo.com

Suggested Reading

1. McCarty DJ. Suppress rheumatoid arthritis early and leave the pyramid for the Egyptians. *J Rheumatol* 1990; 17:1115-8.
2. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, William S et al. A randomized comparative effectiveness study of triple oral therapy versus etanercept plus methotrexate in early, aggressive rheumatoid arthritis. *Arthritis Rheum* 2012; 64: 2824-35.
3. Tosh JC, Walloo AJ, Scott DL, Deighton CM. Cost-effectiveness of combination nonbiologic disease-modifying antirheumatic drug strategies in patients with early rheumatoid arthritis. *J Rheumatol* 2011; 38:1593-1600
4. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2016; 68:1-25.
5. Malaviya A, Gogia S. 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 Apr 28. PMID: 27122121 DOI: 10.1007/s10067-016-3283-0

WHY are Biologicals 'Head and Shoulders' above DMARDs?

Opponent : Shankar Subramanian**

● What are we NOT debating?

1. Are csDMARDs cheaper than bDMARDs as of now? Yes.
2. Are csDMARDs sometimes as effective as bDMARDs when used in RA? Yes, in certain circumstances.
3. Will ALL patients respond only to conventional DMARDs with or without steroids? Definitely not.
4. Are biologics useful when DMARDs fail? Yes.
5. Are biologics being somewhat misused or overused? possibly yes.

● Then what is there to discuss?

Biologicals (bDMARDs) are qualitatively different than csDMARDs. I wish to highlight four aspects:

1. How biologics have redefined the way we perceive RA.
2. The promise of remission.
3. A relook at economics of biologics in the next decade.
4. The future of RA therapy in a decade

● Redefining RA

True, not many rheumatologists used csDMARDs



routinely the way we do so now. Then came biologics and redefined our expectations of disease management. Studies discussed drug free remissions and even the promise of cure. Yes, it came with a high cost, well beyond the reach of most people. This triggered the race

to have a relook at our existing arsenal and a series of studies showed that csDMARDs with low dose steroids could rival biologics in disease control. However, significant qualitative differences still remain.

● The promise of remission

Remission was an unheard of term in RA. Biologics changed all that. Remission while on treatment was being achieved in a majority and drug free remission was being documented in a subset of patients. Table 1 summarises some studies that looked at remission in RA

Registry data support the above observation.

(...continued on page 7)

Study	TVDC	Included	What it did	Findings
BeSt (Behandel-Strategien)	Compared 4 strategies for inducing remission	Early RA	In patients with sustained remission for over 6 months, DMARDs tapered and finally stopped	Arm with methotrexate and infliximab achieved highest drug free remission in > 25%
PRIZE	RCT: Methotrexate plus etanercept Vs standard of care	Early RA	to achieve remission	60% achieved remission, At 1 year 40% : Etanercept free remission 23% all drug free remission
STRASS	Spacing of TNF blocker injections in RA	RA	DAS driven spacing out of TNF blockers in 137 patients according to the treat to target paradigm	3.9% could stop TNF inhibitor in the tapering arm while maintaining the remission
RRR study (Remission induction by Remicade in RA)	Follow up study	RA patients in remission as well as LDA over 24 weeks	Evaluate DAS 28 in 102 patients at 1 year after stopping Infliximab	55% (n=56) had DAS 28 < 3.2 with 43% (n=44) in remission with no radiologic progression
HONOR study	Follow up study	RA patients in remission after stopping adalimumab	Evaluate DAS 28 in RA patients at 1 year after stopping adalimumab	Adalimumab could be discontinued without flaring in 79% patients with deep remission. 48% maintained remission at 1 year

Table 1 : Studies that looked at remission in RA with biologics

In the Norwegian DMARD registry, about 40% of patients with RA achieved remission (DAS28 <2.6). In the ESPOIR cohort, 50% of the patients with early RA were in DAS28 remission 5 years after disease onset and 65% in LDA. Observations from the CORRONA registry suggest that rapid response to DMARDs is associated with better maintenance of remission when the agents are tapered later on. Rapidity of response is much better with biological DMARDs than csDMARDs.

Specific clinical features have been associated with the risk for relapse. In the RRR study and the HONOR study, cutoff points for a successful discontinuation of TNF inhibitors were a baseline DAS28 value of 2.22 and 1.98, respectively, suggesting that 'deep' remission may be required to keep the biological free remission. In the HONOR study, another baseline factor affecting adalimumab free remission was disease duration, indicating that patients with early RA have better chance to stop TNF inhibitors.

● Economics: the winds of change: arrival of Biosimilars

Two factors are driving the winds of change of pricing of biologics. The first one is the emergence of Biosimilars. As more and more biologics go off patent, biosimilars are entering the market and driving the pricing down, almost by 40-70%.

An aspect not easily visible is the enormous amount of research on small molecules targeting various intracellular pathways like Janus-associated kinases (JAKs), spleen tyrosine kinase (SYK), phosphodiesterase-4 (PDE4), Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3 kinase (PI3K) pathways. Tofacitinib is the most visible face of this army and studies have shown excellent efficacy in RA.

In 2022, Tofacitinib will go off patent.

Thereafter, we will have a host of small molecules that will go off patent sequentially. How does that matter? Well, Tofacitinib and the other small molecules are ordinary chemicals and the ease of manufacturing Vs that of biologicals is akin to difficulty in manufacturing of an ordinary bicycle Vs a Boeing 747 (with all its avionics) respectively. (Fig 1)



● Fig 1: Small molecules Vs Biologics: Complexity of manufacturing compared

Once the drugs go off patent, generics are likely to be priced closer to conventional DMARDs and biologics would have to further revise their pricing. It is my opinion that by the year 2023-2025, the conventional DMARDs and small molecules would be almost similarly priced while biologics will all be available at an order of magnitude lesser than what it is now. The winds of change are already visible in India and the rate will only accelerate in the next few years.

● How would we be treating RA a decade from now?

In less than a decade, we would structure a regimen for RA in a personalised way. The patient would have a high probability of achieving remission within a few months and would have a good chance of even reaching drug free remission. (Figure 2) This would be a very cost effective regimen whichever way we choose to analyse the data as an intense protocol in the beginning with bDMARDs would make cure a reality.

This is not science fiction. Already the last decade and a half has shown us the promise and as newer studies and protocols emerge, the scenario would be the reality.

● A glimpse of future

My argument is simple. As of today, a large percentage of patients come well outside the window of opportunity. When we treat patients rather late in disease, we can hope at best to control the disease and remission and cure are usually out of reach. Also, the current pricing

(...continued on page 8)

of bDMARDs makes it out of reach of a vast majority of Indians. In this scenario, bDMARDs may not offer any great advantage over conventional csDMARDs. However, as the promise of remission and cure becomes more and more real, as the prices come down due to the combination of multiple factors and as patients get diagnosed earlier in the disease, Biologics clearly hold the edge over conventional DMARDs.

Rather than looking at the cost factor alone and viewing bDMARDs through the prism of nihilism and despondency, it is prudent to look at the overall picture. With rapid strides we may well witness RA getting cured!

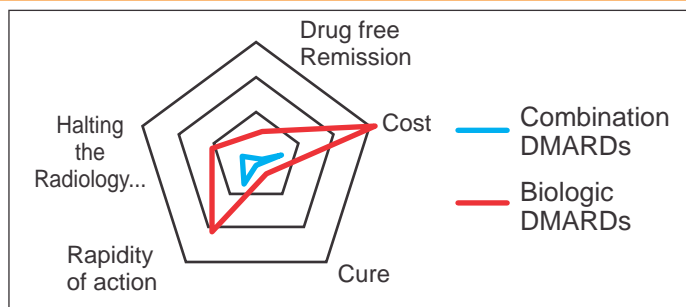


Figure2: Radar chart showing a comparative analysis of csDMARDs and bDMARDs

**Author:

Gp Capt Shankar Subramanian, MD, DNB, MNAMS, FICP FRCP (Hon. Glasg), Professor & Senior Advisor of Medicine, Rheumatology & Clinical Immunology, Medical Division, Command Hospital (Air Force), Bangalore India 50007.

Email: shankarsid@gmail.com

Suggested Reading

1. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJSM, Hazes JMW, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 2005;52:3381-90.

2. Tanaka Y, Takeuchi T, Mimori T, Saito K, Nawata M, Kameda H, et al RRR study investigators. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis.* 2010 Jul;69(7):1286-91

3. Tanaka Y, Hirata S, Kubo S, Fukuyo S, Hanami K, Sawamukai N, et al. Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. *Ann Rheum Dis.* 2015 Feb;74(2):389-95.

Why bDMARDs will hold an edge over csDMARDs in the next decade

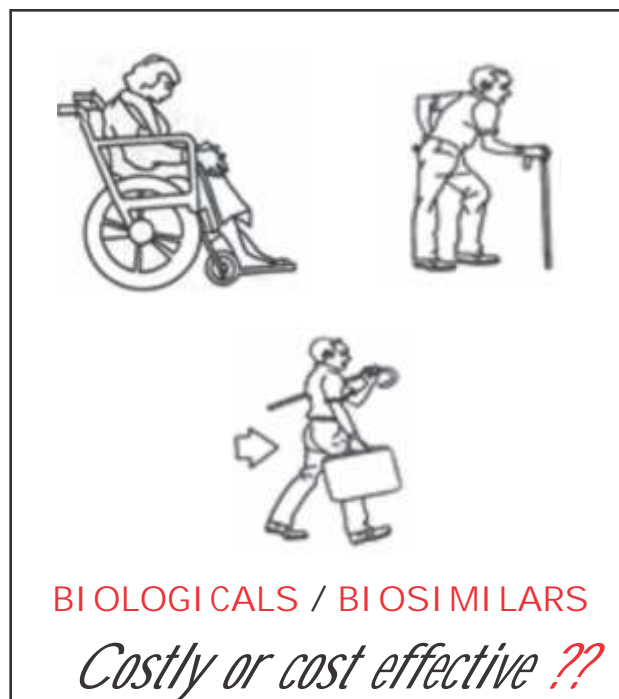
- bDMARDs offer a definite chance of drug free remission and of possible cure in early RA, albeit in a small percentage.
- Prices of bDMARDs will come down by over an order of magnitude due to multiple factors in the next 5-6 years, making them competitive Vs csDMARDs

● **Debate Proponent :**

Professor Anand N. Malaviya. MD, FRCP (Hon. Lond), Master-ACR, FACP, FICP, FAMS, FNASc; (Rtd. Chairman, Dept. of Medicine, and Chief of Clinical Immunology & Rheumatology Services, AIIMS; (Presently): Head of the Department of Rheumatology, ISIC Superspeciality Hospital. New Delhi, India

● **Debate Opponent :**

Gp Capt Shankar Subramanian MD, DNB, MNAMS, FICP FRCP (Hon. Glasg), Professor & Senior Advisor of Medicine, Rheumatology & Clinical Immunology. Medical Division, Command Hospital (Air Force), Bangalore, India



VoA E-in-C recommends a must read:

“Can We Get Closer to a Cure for Rheumatoid Arthritis ?”

by Prof. Marc Feldmann and Sir Ravinder Maini :

“We have new powerful tools and much more knowledge. Do we have the ambition and the will?”

“Arthritis & Rheumatology” : Vol.67, No.9, September 2015, pp 2283-2291



Antiphospholipid the Hughes Syndrome : Story retold Prakash Pispati*

1975: Jamaica - Kingston visited earlier by Her Majesty Queen Elizabeth, late Princess Lady Diana ... and the first James Bond (remember the film, 'Dr.No' ? featuring a nuclear reactor and Ursula Andress on the beach?). Yes, that's where Rheumatology took off in the West Indies as Professor Graham Hughes was invited to set up a rheumatology clinic in the University of the West Indies (1975). That's where it all started. He noticed something unusual in lupus patients there : a form of tropical paralysis called Jamaican neuropathy. In his own words "This disastrous spinal paralysis, not known to be due to a virus, showed some interesting parallels to lupus, with anti-nuclear antibodies, and, more interestingly, with antibodies directed against phospholipids – molecules important in the structure and composition of the nervous system. We hypothesized that antiphospholipid antibodies might interfere in brain tissue and might directly result in disease." (From the book Hughes Syndrome – 'A Patient's guide').

On return to Hammersmith Hospital and subsequently St. Thomas', England, he found these antibodies were clearly associated with thromboses, often affecting placenta inducing miscarriages. With his team he identified such manifestations in lupus and later even without lupus in patients. His team set up assays to detect such antibodies.... putting all together the term coined Anticardiolipin, renamed Antiphospholipid syndrome, later rechristened the Hughes' Syndrome. The complex association of bizarre clinical manifestations included frequent clotting episodes such as deep vein thrombosis, likewise strokes and miscarriages. So he simply called



Prof. Graham Hughes and Prakash Pispati at Jaslok Hospital, Mumbai 2005
this "sticky blood disease". Rheumatologists by now the world over are fairly familiar diagnosing and treating such patients. (Fig.)

Surely not every patient presents such obvious features. Confusing incomplete forms may be dubbed 'half diagnosis'. To such patients it is helpful to pose questions:

- Have you noticed a clot in any of your blood vessels ?
- Do you suffer from migraine ?
- Do any of your blood relatives have an autoimmune disease (eg. RA, SLE, Vasculitis)?
- Any miscarriages at all ? (Obstetric history a must in every patient).
- Hope you never had a stroke, transient blindness ?
- Have you had a seizure ?
- Have you had a spontaneous fracture ?

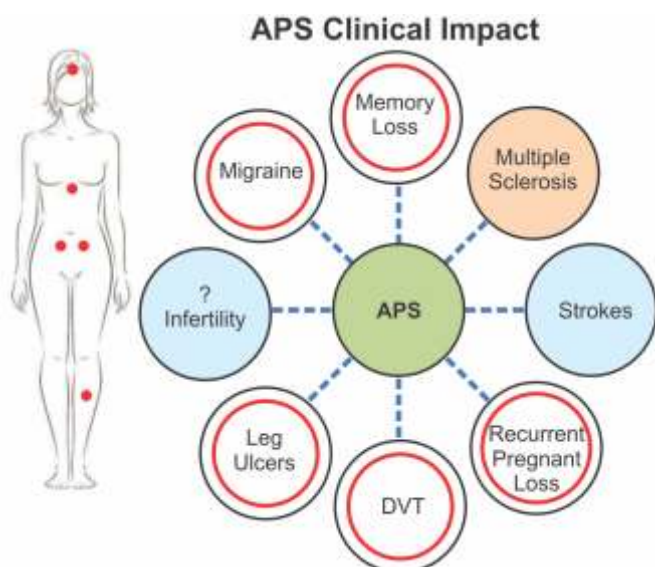
Professor Hughes in his lucid talks has given his formula : 1 in 5 Young strokes

1 in 5 DVT

1 in 5 Recurrent miscarriages

Listening to his lectures is like going to a concert. His deep probing mind harmonizing clinical acumen with laboratory investigations is impressive. The world over now tests for APS in Rheumatology and Obstetric clinics are almost universal.

(..... continued on Page 10)



Yet, Graham cautions against over reliance on the laboratory. Negative test results may belie absence of APS. In as much as we recognize seronegative RA, seronegative lupus, so also we should acknowledge Seronegative APS, he advocates.

In a patient with obvious clinical features of APS yet with no detectable aCLA / LAC, what are we to do? Worry far too much about revised SAPPORO criteria? Dismiss the diagnosis of APS? Not quite. A message to remember: Should we be convinced that if the patient has obvious clinical manifestations of APS, don't wait, start treating carefully preventing iatrogenic complications. So far so good.

● What lies ahead ?

Prof. Hughes predicts :

- aPL testing will become worldwide and routine in rheumatology, neurology, Ob – Gy;
- Over-the-counter aPL testing kits will become available to calibrate INR with anticoagulants;
- A substantial subset of migraine sufferers will fare better;
- APS will be recognized as a major link between migraine and stroke;
- Heart attacks in the youth will be reduced;
- Strokes in those under 45 will be minimized
- Biologicals eg. rituximab play a defined role.
- APS will impact our clinical assessment and the way to treat lupus;
- The incidence of miscarriages / stillbirths will be minimized, thanks, to a more proactive approach.

● The Challenge:

Will newer biomarkers, newer diagnostic tests be verified, simplified and be within reach of most Asians for early detection, prevention and treatment of APS? Do newer anticoagulants justify their high costs to replace time trusted LMW Heparin, and Warfarin? Yet a disturbing question persists. Must such unfortunate patients of APS i.e. Hughes Syndrome be treated lifelong perilously with rather dangerous lifelong anticoagulants with patients on a thin edge of clotting vs hemorrhage?... say in a remote clinic? For the present this seems inevitable, yet with due

care and expertise thousands of patients have survived and are enjoying fulfilled family lives. Yet futuristic research must address this perturbing practical question.

● Epilogue:

Understanding the Hughes Syndrome has facilitated lives of our patients of such a complex disease with enhanced success rates. Not without reason, the late Princess Lady Diana visited Professor Graham Hughes at his Lupus Clinic at Hammersmith Hospital (subsequently moved to St. Thomas' Hospital, right across the river from Big Ben).



Late Princess Lady Diana with Prof. Hughes, London

* Author:

Prakash Pispati, M.D., F.R.S.M. (Lon)

Editor-in-Chief: Voice of APLAR

Email: prakashpispati@vsnl.net; prakashpispati@gmail.com

Director of Rheumatology -

Jaslak Hospital & Research Centre, Mumbai, India.

Sr. Consultant Rheumatologist - Saifee Hospital, Mumbai.

Master, Honary Member & Past President : APLAR

Past President : Indian Rheumatology Association

International Fellow Member: ACR

Recommended reading:

1. Hughes Syndrome – A Patient's Guide by Graham Hughes - Springer.
2. Graham RV Hughes. APS, Not Just Thrombosis & Miscarriage. *The Rheumatologist*. 2016;10 (2)1, 13-17
3. Graham Hughes, ed. Hughes Syndrome: a patient's guide. Springer-Verlag, London: 2001
4. Vishad Vishwanath, Debashish Danda. Update on Antiphospholipid Syndrome. In: Rao URK ed. Manual of Rheumatology, 4th ed : Indian Rheumatology Association; 2014: 269 – 290.
5. Gaëlle Guettrot-Imbert, Nathalie Costedoat-Chalumeau, Angela Tincani. In : Johannes WJ Bijlsma, Eric Hachulla eds. EULAR Textbook on Rheumatic Diseases, 2nd ed: BMJ Publishing Group, London ; 2015: 577 - 605.

Syrian Association for Rheumatology (SAR)

Syrian Association for Rheumatology (SAR) held the following activities in 2015-2016:

September 2015: 21st SAR Symposium on Metabolic Bone Diseases, Damascus.

January 2016: Scientific Day on Osteoarthritis organized jointly by the SAR and Department of Internal Medicine at The Assad University Hospital.

February 2016: 22nd SAR Symposium "Update on Systemic Lupus Erythematosus" held in Damascus.

6th October 2016: 23rd SAR Symposium titled "Eight Topics Update in Rheumatology".

Gutsy Syrians! GOOD WISHES! ... E-in-C



Prof. Gerd Burmester
 President of EULAR,
 European League Against Rheumatism



It is a real pleasure for EULAR to welcome "Voice of APLAR", a quarterly e-Bulletin for all APLAR members, and hopefully also for its sister leagues world-wide. Communication is the core of our organisations and the digital area makes it more feasible than ever. We are looking forward to an interesting and stimulating e-Bulletin and will be happy to share EULAR news with you, such as the start of the EULAR School of Rheumatology in early 2017, the year of the 70th birthday of EULAR. We wish the Voice of APLAR and its editorial team a very good start and a bright future.



The American College of Rheumatology congratulates APLAR on the launch of its new quarterly e-Bulletin, Voice of APLAR, and sends best wishes for much success.



left to right: Dr. Sharad Lakhanpal - President Elect, Dr. Joan M. Von Feldt - President, and Dr. E. William St. Clair - Immediate Past President.



India was one of the founding members of APLAR and over the years APLAR has grown into a fine professional body looking after interest of Rheumatology in Asia-Pacific where more than 60% of the World population stays. I would like to congratulate APLAR for bringing out Voice of APLAR as it will truly help spread the voice of APLAR to all its members in a simple language. Indian Rheumatology Association is proud that one of our members is the Editor-in-chief of this new venture. I hope Voice of APLAR will be a game changer and would also include patient and society perspective.

All the best,
Prof. Amita Aggarwal, President,
Indian Rheumatology Association



College of Specialists in Rheumatology & Rehabilitation, Colombo, Sri Lanka

We are proud to announce the formation and inauguration of College of Specialists in Rheumatology & Rehabilitation in Sri Lanka following rapid recent growth in the field and an enduring commitment to the highest standards of care. The members of the Sri Lankan Association of Rheumatology and Medical Rehabilitation unanimously moved to establish the College to replace the Association at an Annual General Meeting held on the 28th of May this year in the historical city of Kandy.

Our Association was admitted to APLAR in 2001 with the assistance of Dr. Pispati. The Arthritis Foundation, which serves as a bridge between Consultants and the community was established in 2004. A strong

collaboration with Swedish Rheumatism

Association led to the formation of patient groups. World Arthritis Day was celebrated for the first time in Sri Lanka in the same year.

A tree that is slow to grow bears the best fruits, and similarly our college is slowly setting up on a firm foundation that will strengthen the field of Rheumatology and Rehabilitation in years to come.

Inaugural Conference: October 22, 2016, Colombo.



Achievements and Potential of Rheumatology in China

In the last few decades, rheumatology in China has been developing rapidly in various areas with substantial achievements with over 5000 rheumatologists. Rheumatology research in China has resulted in several decent publications even in Nature Medicine, Nature Genetics, Immunity, Cell Host Microbe, Arthritis and Rheumatism and Annals of Rheumatic Diseases enhancing international collaboration and academic exchanges between China and developed countries. While China



has hosted many international conferences, our Rheumatologists have been attending EULAR, ACR, APLAR, PANLAR and many other conferences overseas. We will move forward with the world....

In Chinese "Collaborate and win together"



Prof. Zhanguo Li - MD, PhD
Chief, Department of Rheumatology and Immunology, Beijing University People's Hospital.
Immediate Past President, APLAR

Tribute to a Legend - Professor Feng Pao Hsii, Singapore

(31 October 1936 -19 December 2015)

Professor Feng began his medical career as a trainee in Nephrology in 1969 in Israel. He developed a special interest in the disease of Systemic Lupus Erythematosus (SLE) when he cared for Lupus patients. In 1982, with great foresight and wisdom, he initiated the training of the first Singaporean doctor (myself) under Professor Graham Hughes in the Department of Rheumatology, Hammersmith Hospital, London. Indeed, he is lovingly called the "Father of Rheumatology".



Conference on SLE and the XIX ILAR Congress of Rheumatology in 1997. He undoubtedly placed Singapore on the world map of Rheumatology. He touched the lives of many rheumatologists in many nations with his candid talks, ideas and collaborative efforts.

Professor Feng networked extensively with the International Rheumatology community. In 1989 Singapore hosted the Second International

Dr Boey Mee Leng
Consultant Rheumatologist, Singapore

APLAR is indebted to the late Professor Feng to consolidate our journal IJR. His editorials were incisive and delightful to read. He was at his best hosting excellent conferences ...
Prakash Pispati, E-in-C, VoA.

VoA invites YOU to write: On the broad canvas of Rheumatology, Medicine and Life

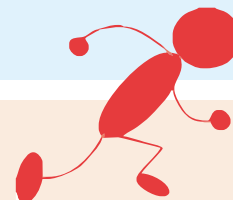
- Thought provoking Essay • Challenging case • Anecdote, Satire, Cartoon • Debate • Travelogue • Events, News and Views • Letters, Suggestions, Complaints
- Please recommend advertisement /

Sponsor a page by your National Society / drug company

Email: prakashpispati@vsnl.net ; prakashpispati@gmail.com

VoA : Editorial Team (in formation)

Editor-in-Chief	: Dr Prakash Pispati.
Associate Editor	: Gp Capt. Dr Shankar Subramanian,
Editorial Board	: Dr Kevin Pile, Dr K Yamamoto, Dr Zhanguo Li, Dr D Danda, Dr Yue Yang
Design & Layout	: Tushar Prabhoo, Prakash Pispati, Mumbai, India.
Secretarial	: Ms. Christine Rebello



All material published in this e-Bulletin represent the opinions and views of the authors and not necessarily of APLAR or its editorial team. Material published in this e-Bulletin are intended for information, understanding and discussion only and should not be relied upon as recommending a specific diagnosis or treatment. APLAR and its Editorial team accepts no legal responsibility for any errors or omissions and make no warranty with respect to material contained herein. The Editorial team of this e-Bulletin does not guarantee or endorse any commercial product or service. Copyright, no articles or its part may be published without permission of the Editor-in- Chief. email: prakashpispati@gmail.com ; prakashpispati@vsnl.net Mumbai, India