CHAPTER

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Remission in Rheumatoid Arthritis: A Reality in 2017

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REMISSION IN RA

Remission was an unheard of term in Rheumatoid arthritis (RA). Developments in the last decade or so that have looked a combination of factors have changed all that. Remission while on treatment is being achieved in a significant percentage of patients and drug free remission is being documented in a noteworthy subset. In the words of Prof Rohini Handa, the letters "6T" model captures the essence of all this development. (Figure 1)

TIME TO TREAT

The earlier we control of inflammation in RA, the better is the outcome. The current treatment strategy is to make diagnosis early, be aggressive with therapy after establishing the diagnosis, and aim to reach clinical remission. "Hit early, hit hard" should be the motto. The therapeutic response in the first 3 months of therapy predicts the potential of reaching remission later. Many studies have shown that aggressive treatment in the early phase of the disease leads to excellent improvement and sustained benefit. The early phase of disease thus presents a "Window of Opportunity" that is characterized by reversible autoimmunity offering an increasing chance of remisison.

Currently we have a vast repertoire of synthetic (sDMARD) and biological disease modifying antirheumatic drugs (bDMARD) that can enable us to achieve remarkable improvement is achievable in clinical outcomes, including remission.

The ACR/EULAR 2010 criteria to diagnose RA enable early diagnosis within a few weeks of onset of disease that was not possible with the earlier 1987 crtieria. The American College of Rheumatology (ACR) 2015 guidelines for the management of RA have laid down a evidence based blueprint for effective RA management that can help in achieving this aim.

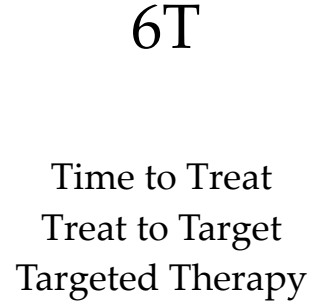

Fig. 1: 6T model to manage RA effectively

TREAT TO TARGET: STRATEGY VS CHOICE OF DRUGS

In addition to the advent of bDMARDs, the last decade witnessed many "Strategy" trials. These studies looked more at reaching a predefined target rather than focus on the drugs used to achieve these targets. Trials like the TICORA, Dutch DAS-driven care, and CAMERA trials were predominantly strategy trials that compared a protocol-driven intensive strategy to usual care. Other trials like BeSt, CIMESTRA, TICORA 2, Step-down versus step-up, and TEAR trials were hybrid in nature, in that an initial parallel design was supplemented with incremental protocol-driven intensification of treatment.

All of these trials showed that a strategy of aiming for low disease activity or remission appears more important than the choice of a specific agent. The key lesson being that routine monitoring with an index should be the norm in patient care at each visit. The choice of the index is not of much importance. One may use DAS28, CDAI, SDAI or any of the several others.

TARGETED THERAPY: THE PROMISE OF REMISSION

The advent of bDMARDs has redefined our expectations of disease management. Table 1 summarises some studies that looked at remission in RA.

Registry data support the above observation. In the Norwegian DMARD registry, about 40% of patients with RA achieved remission. In the ESPOIR cohort, 50% of the patients with early RA were in DAS28 remission 5 years after disease onset and 65% in LDA. Rapidity of response is much better with biological DMARDs than csDMARDs.

DEFINING REMISSION

Remission has been defined variously using different indices, some quite strict like the American Rheumatism Association (ARA) definition, SDAI or CDAI while others are quite loose like DAS, DAS28, modified ARA and MDA. A few indices are based purely on patient reported outcomes (PRA).

Remission is a basically a state characterized by absence of disease activity. The new ACR-EULAR 2011 definition (Figure 2) is a comprehensive attempt to define remission.

A recent systematic review looked at 18 studies and identified factors that best predicted remission in RA (Table 2)

BIOLOGIC FREE AND DRUG FREE REMISSION

Early treatment offers the best chance of drug free remission. In the BeSt study, 48 % of patients were in

Table1: Studies that looked at remission in RA with biologics

S No	Study	Type	Included	What it did	Findings
1	BeSt (Behandel-Strategieën)	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%
2	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
3	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	39% could stop TNF inhibitor in the tapering arm while maintaining the remission
4	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
5	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 2: Factors associated favourably with remission

- Male sex
- young age
- late-onset RA
- short disease duration
- nonsmoker
- low baseline disease activity
- mild functional impairment
- low baseline radiographic damage
- absence of rheumatoid factor and anti– citrullinated peptide
- low serum level of acute-phase reactant, interleukin-2, and RANKL at baseline
- MTHFR 677T alleles and 1298C alleles in the methotrexate (MTX)–treated patients
- early treatment with s DMARD combinations
- the use of anti–tumor necrosis factor (anti-TNF)
- the concurrent use of DMARDs in anti-TNF–treated patients
- moderate or good response to treatments at the first 6 months

ACR-EULAR 2011 Definition of Remission

For clinical trials

- Boolean
  - SJC, TJS, PtGA, CRP all ≤ 1
- Index-based
  - SDAI ≤ 3.3

SDAI = SJC + TJC + PhGA + PtGA + CRP (mg/dl)

For clinical practice

- Boolean
  - SJC, TJC, PtGA all ≤ 1
- Index-based
  - CDAI ≤ 2.8

CDAI = SJC + TJC + PhGA + PtGA

Fig. 2: ACR-EULAR definition of remission

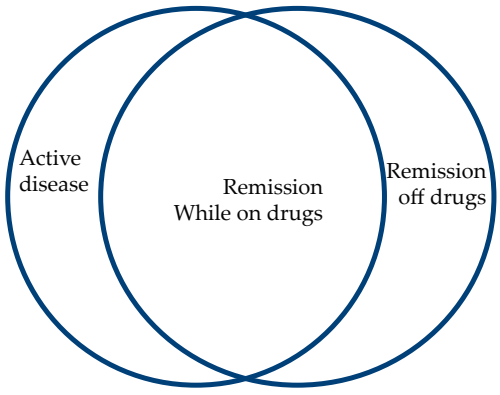

Fig. 3: A schematic representation of remission

remission and 14 % in drug-free remission after 5 years. Drug free remission is what patients associate with "Cure". (Figure 3) Though currently this number is modest (being under 20%) in most studies however, the future seems promising with our better understanding of RA pathogenesis, better strategies and newer molecules.

Biologics hold an edge over conventional DMARDs, esp in the promise of inducing drug free remission. (Figure 4). They are however priced almost a 100 times more (Rs 5000 Vs Rs 4-500000 per annum) and are currently unaffordable to the majority. The next decade is likely to witness a better price rationalization due to a variety of factors making biologics accessible to many.

ECONOMICS: THE WINDS OF CHANGE

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%.

A 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), and Bruton's tyrosine kinase (BTK). 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 (Figure 5).

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 can be expected 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. 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.

As of today, a large percentage of patents 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 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, remission becomes a reality.

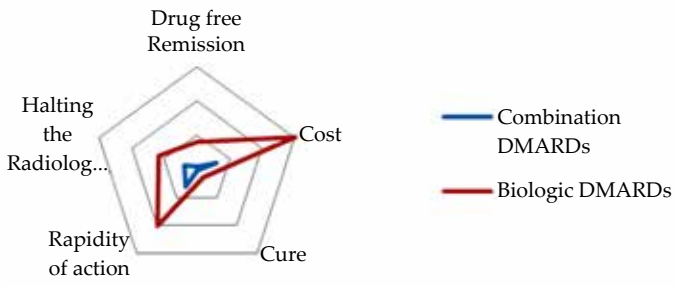

Fig. 4: Radar chart showing a comparative analysis of csDMARDs and bDMARDs

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Fig. 5: Small molecules Vs Biologics: Complexity of manufacturing compared

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