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Biotechnology Solutions for Inflammatory Arthritides — RA and SPA

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FRUSTRATIONS OF A PHYSICIAN

At the turn of the 19th century, Sir William Osler wrote rather depressingly:

"ARTHRITIS DEFORMANS

Once established, the disease is rarely curable. Too often it is a slow, but progressive crippling of the joints, with disability that makes the disease one of the most terrible of human afflictions.

—W. Osler, 1909, Principles and Practice of Medicine"

At the turn of the 20th century, biotechnology medicines *inducing rapid remission* became a practical reality. Inflammatory rheumatic diseases, notably rheumatoid arthritis and spondyloarthropathies, are notorious for their chronicity. Did we doctors make them *more* chronic by *going slow, going low?* Even today one hears that one is not prescribing vigorous treatment unless there is an emergency. We seem to have grossly underestimated the impact of arthritis on our patients and their lives (see box).

RA / SPA

- Afflicts young and old, men and women, sparing none.
- Certain to result in one or more deformities left untreated or treated inappropriately.
- Devastates/cripples the patient, and the family
- The patient often rendered jobless, virtually homeless
- High morbidity, crippling deformities, expensive corrective surgeries
- Serious complications, medical and non-medical
- Reduced life expectancy around 10 years

FROM NSAIDs, DMARDs TO NEW BIOLOGICALS

For centuries, relief of pain drove the patient to the doctor, and the doctor hither and thither seeking drugs and even magic remedies. The result? Chaos! Historically, traditional medicine often with religious flavors gave birth to some world recognized systems such as ayurveda, homoeopathy, unani. Also, unfortunately, to quackery!

In our own discipline, generally called allopathy, we sought pain relief by using willow bark, i.e. the Aspirin. The first paper on Aspirin was published by Von Felix Hoffman in 1897. Since then, we have had a plethora of NSAIDs reaching their heyday in the 1970s-80s. The mantra then was 'relieve pain, reduce swelling'. Then came the first paper on cyclophosphamide in 1970 and then methotrexate in 1985 by Michael Wienblatt, a landmark introduction of methotrexate in rheumatoid arthritis. Well before that were antimalarials and sulfasalazine which were then used.

Today, nearly all of us use DMARDs, albeit often starting late enough and in doses low enough to virtually sustaining inflammatory chronicity, unwittingly producing rather than preventing deformities. Corticosteroids, a discovery in RA patients, is a great story to tell. Unfortunately, so much abused, misused and often not used at all when they should be.

Are we physicians then mastering the art of using our drugs the way they should be? While relieving pain, have we actually produced rather than prevented deformities and sustained miseries of our patients?

BIOTECHNOLOGY SOLUTIONS: A CHALLENGE MET

In the 1980s Maini and Feldmann clearly identified Tumour Necrosis Factor (TNF) as a culprit cytokine that

sets in motion the inflammatory cascade, producing joint destruction. Specific monoclonal antibodies to TNF dramatically and most commonly are now so well known to induce rapid remission in inflammatory arthritis.

TARGETED THERAPIES

Infliximab and Etanercept are the two biological agents used increasingly and with enhanced success in India. Infliximab is given intravenously 3-5 mg/kg body weight on day-0, day-14 and every 6-8 weeks. Etanercept is given subcutaneously 50 mg once a week. Cost constraints prevent physicians in India to use them for longer periods. Nevertheless, they induce rapid remission, relieve pain virtually vanish early morning stiffness, induce a sense of well-being, enthusiasm, confidence, while restoring mobility and, in other words, mobilizing the crippled. Sometimes this can happen within days, certainly within a few weeks. Truly dramatic are the results.

A newer biological available is Adalimumab which blocks interleukin-1 not available in India, so do not have personal experience. In those who do not respond to TNF blocking drugs, this would probably be the answer. Another biological being launched in India is Rituximab. (see box)

MONOCLONAL ANTIBODIES FOR RA, SPA

- Infliximab
- Etanercept
- Adalimumab
- Abatacept
- Rituximab

Infliximab (a chimeric (mouse/human) IgG1 monoclonal antibody, which neutralizes the biological activity of TNF-α [but not TNF-β (lymphotoxin a by binding with high affinity and specificity to the soluble and transmembrane forms of TNF-α—thereby inhibiting further receptor binding). The recommended dose of infliximab is 3 mg/kg given intravenous infusion, followed by additional 3 mg/kg doses at 2 and 6 weeks, then 8 weekly thereafter.

Etanercept (a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) TNF receptor linked to the Fc portion of human IgG1), produced by recombinant DNA technology. Etanercept binds to TNF-α and TNF-β and blocks interaction with cell surface TNF receptors, thereby rendering TNF biologically inactive). The recommended dose is 25 mg twice per week given subcutaneously, or 50 mg once a week.

Adalimumab (fully human) IgG1 monoclonal antibody which binds to TNF-α. The recommended dose is 40 mg given subcutaneously fortnightly.

A newer biological available which blocks interleukin-1, anakinra is also used, not available in India.

Abatacept is a co-stimulator blocking agent approved in the USA, not available here.

RHEUMATOID ARTHRITIS

TNF blocking agents administered in the right dose, the right way, at the right time for RA, PsA, AS, and juvenile RA, should lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 12 weeks. There is no evidence that of any one TNF blocking agent should be used before another one can be tried, just as there is no credible evidence that any TNF blocker is more effective than any other in RA. Patients have been switched from one TNF blocking agent to another, but no well-controlled switch trials have been published. These studies suggest that failure to respond to one TNF blocking agent does preclude response to another.

Individually important response including patient oriented measures (e.g. HAQ-DI, patients global VAS, Medical Outcome Survery Short Form 36 (SF-36) or physical measures (for example, joint tenderness) should be demonstrated within 12 weeks for RA, PsA, AS and probably, JRA. If such improvement occurs, treatment should be continued. If patients show no response to these agents, their continued use should be re-evaluated. Observations suggest that increasing the dose or reducing the dosing intervals may provide additional benefit in RA, as may the addition or substitution of other DMARDs. However, because regression to the mean may occur, caution is needed when interpreting apparent improvements following dose escalation in practice.

There are data showing that TNF blocking agents slow radiographic progression in RA and in PsA. In some individuals, TNF blocking agents may inhibit radiographic progression. Although some RA patients without clinical response have slowing radiographic progression, the long-term clinical implications of these changes are unknown. Until the long-term implications of slowing radiological damage are clear, radiological effects alone should not determine clinical decision making. Magnetic resonance imaging ((MRI) is

beginning to be used to document response in RA although it is not yet a fully validated technique for this purpose.

SPONDYLOARTHROPATHIES (SPA)

This fascinating group of diseases include ankylosing spondylitis, psoriatic arthritis and reactive arthritis, all seronegative. Here again, there is a paradigm shift to inducing rapid remission, preventing deformities, mobilizing the crippled as much as possible.

Ankylosing Spondylitis

A graveyard of all drugs so far. Those which failed are the pain-killers such as aspirin, paracetamol, NSAIDs, disease modifying drugs such as antimalarials, gold injections, sulfasalazine (except for peripheral joints) and methotrexate. The only treatments that probably work well are the biotechnology medicines. In India, we have fair experience with infliximab and etanercept

Individually important responses including patient oriented measures (for example, BASDAI, BASFI, patient global VAS, SF-36) or physical measures should be demonstrated within 12 weeks for AS.

Psoriatic Arthritis

Psoriatic arthritis is a notorious disease. Another graveyard of many drugs. Patients, both male and female, respond rapidly. Biological medicines not only work dramatically, but the patients equally well perceive their benefits. Mobility is restored quickly, and skin lesions decrease significantly between a few weeks to a couple of months.

Individually important responses including patient oriented measures (for example, patient global VAS, DAS 28, SF-36) laboratory or physical measures (for example, joint tenderness) should be demonstrated within 12 weeks for PsA. Data show that atleast adalimumab and etanercept may slow the appearance of new erosions in PsA . Analyses also using other, as yet not validated radiographic measures, also demonstrate inhibition of radiographic damage in PsA.

BIOLOGICALS: PRACTICAL CONSIDERATIONS

- When should they be initiated? ASAP, i.e. as early as possible. Let us not wait. The modern mantra is to pick up early RA and treat it early, aggressively, with biologicals whenever possible, at least to induce therapy and in combination with methotrexate. The window of opportunity to prevent deformities at the very start is mere *two months*. Bioliogicals will prevent the onset of deformities, may even reverse them partially, especially if started early enough.
- What is the first step? Make sure of the diagnosis, fulfilling criteria of American College of Rheumatology and not get confused too much about positivity or otherwise of rheumatoid factor, if necessary, ordering anti-CCP.
- Ensure that there is no concurrent infection, especially of TB. The screening procedures to include a Mantoux test, X-ray chest and the usual baseline investigation like ESR, CBC. Let us not get confused by the positivity or otherwise of Mantoux test (PPD).
- Take some slight risk or may be a history of old Koch's lesions in the chest. Take some slight risk to initiate biologic treatment, and give isoniazid prophylaxis at the same time.
- In the event of infection flareup, discontinue biologicals, treating appropriately with antimicrobials, if TB is thought of, then 3-4 anti-Koch's regime.
- *Predicting, preventing and managing adverse reactions*

RISKS OF TNF-ALPHA-INHIBITION

- Infections
- Increased number of septic joints ?
- Effects on healing of wounds ?
- TNF: ↑ Granuloma formation, ↓ Mtb
- TNF blockade: latency to reactivation
- New strategy: Inflammation ↓↓↓
  Anti infection ↑↑↑

Nothing in the world is without side-effect. Biologicals are a lot safe than DMARDs and NSAIDs. The reason? They are *specific* monoclonal antibodies so will not act anyway other than blocking TNF. So there is no vital organ toxicity and no generalized side-effects. Since they are proteinic in nature, allergic reactions including anaphylaxis can occur, yet manageable.

TNF blocking does not increase proneness to infection. TNF is certainly protective especially to the host facilitating T-cells to engulf in destroying microbacterial TB. Hence the risk of aggravation of TB. Hence the need for a screening proper procedure for TB.

- Perform TST
- Chest radiograph
  - — If TST result positive
  - — If clinical or epidemiological suspicion
  - — Possible role for interferon-gamma (INF-g) release assays in future

BIOTECHNOLOGY: TODAY'S MEDICINE

Monoclonal antibodies have paved the way for definite control and remission of inflammatory arthritis. Even other inflammatory diseases called *orphan diseases* are controlled, such as Sjögren's disease, dermatomyositis, polymyositis and juvenile idiopathic arthritis. Vasculitis has shown good responsiveness to TNF blocking drugs.

The concept has resulted in control of systemic lupus erythematosus by another biotechnology medicine Rituximab. Within a few weeks this dreaded disease can also be controlled.

We need to understand biologicals far more, use them, cultivate hands-on experience in our environment, in our patients and master them. Aldous Huxley in his book 1928 Brave New World predicted 'magic bullets' to control complex diseases; they seem to have arrived.

India is among the few countries which has consolidated biotechnology research contributing to evolving biotechnology solutions. The control of inflammatory arthritis is a great contribution of rheumatology to general medicine of today and tomorrow.

SUGGESTED READING

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