

EPILOGUE

The 2005 International Symposium on Advances in Targeted Therapies: What have we learned in the 2000s and where are we going?

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This essay summarises a personal perspective on where we have got to in the five years since the turn of the last century. The focus is on advances in knowledge of antitumour necrosis factor (anti-TNF) therapy of rheumatoid arthritis and other chronic immune-inflammatory rheumatic diseases. The accumulating knowledge is clarifying the scope and limitations of efficacy, safety, and durability of these agents. It is defining the unmet needs of patients and communities worldwide for the future. The call is for progress in providing more cost-effective advances in therapeutics that not only interrupt the disease process long term but also reverse the anatomical and functional consequences of disease and the impairment in quality of life.

This year, it is my privilege to end this annual retreat, which some would justifiably claim is the most significant meeting bringing updated information on biological targeted therapies to representatives of major stakeholders in the enterprise. It is a tribute to Joseph Smolen, Ferry Breedveld, and Jochen Kalden that the meeting continues to flourish and enjoys the support it does. Clearly it serves a much desired purpose, not least the development of a consensus on the best use of new and expensive therapies for the chronic diseases that greatly impact on the quality of life of many patients worldwide.

I have been charged with the task of reviewing progress over the past five years. In some respects, it seemed to me that the remarkable predictability of anticipated progress makes me question if anything new has emerged? Upon surveying the landscape, however, I concluded that the main progress is in the clinical research field. Antitumour necrosis factor (anti-TNF) agents have remained the focus of accumulating detailed new knowledge and substantial evidence on which to base our rational decisions in clinical practice. More importantly, the past five years allow us to set the agenda for future research. At this meeting we have been hearing of emerging new concepts and technologies that will drive the discovery process forwards. Only the most sceptical would question that the exciting new work in biology, attracting the most talented people, some represented here today, will fail to yield results that will move into the translational arena of medicine in the near future. That it will change the lives of patients for the better is a hope which will continue to motivate research scientists and industry. Paraphrasing the words of the late Harold Wilson, British Prime Minister in the 1960s, on the role of science in society, it is a future “that is going to be forged in the white heat of this revolution ...”.

EXPANDED INDICATIONS AND SIMILARITIES OR DIFFERENCES BETWEEN ANTI-TNF AGENTS

In the decade beginning in 1992 when 20 patients with rheumatoid arthritis (RA) were exposed to a chimeric monoclonal anti-human TNF α antibody, cA2 (infliximab) with exciting results, three anti-TNF biologicals—etanercept, infliximab, and adalimumab—have become established as effective therapeutics. By 2005 almost a million patients are estimated to have been treated with these biological drugs, the majority for RA. As has been summarised at this annual symposium, new indications which have been validated since 2000 include ankylosing spondylitis, psoriasis, and psoriatic arthritis. Given the heterogeneity of patient populations recruited in clinical trials with these disorders and of differences in protocol, the remarkable similarity of results underscores the hypothesis that the pharmacological basis of action is related to the neutralisation of TNF α bioactivity at disease sites.

However, there appear to be differences in the clinical efficacy and safety profiles, which raise questions that remain unanswered thus far. The lack of efficacy of etanercept, for example in Crohn’s disease, compared with impressive efficacy of infliximab (and apparently adalimumab), could arguably be related to the constraints of molecular interaction of the anti-TNF drug with TNF, imposed by differences in the structural construct of an antibody molecule versus a dimeric receptor fusion protein. It has been postulated that such differences could result in subtle differences in biological function of interaction at cell surfaces (for example, resulting in apoptosis or regulatory function) that do not occur in the fluid phase. The same concept has been advanced to explain the apparently higher incidence of reactivation of latent tuberculosis by the two antibody therapeutics compared with the fusion protein. However, the differences may lie in achieving critical differential concentrations of the therapeutic at the target site in achieving a clinical endpoint, rather than a physio-chemical property of the construct per se. The former possibility would require much higher doses of etanercept to demonstrate equivalence, and this has not been tested.

Other clinical observations which suggest differences reported since 2000, arise from reports of efficacy using an alternative anti-TNF agent when the original one has failed. When this efficacy arises as a secondary failure due to tachyphylaxis or induction of neutralising antibodies, the difference in structure and immunogenic epitopes could well explain the observation. Indeed, this may be the case following a sequential use of infliximab and adalimumab and vice versa. A study of epitope specificity of neutralising antibody would strengthen the case for this explanation. However, the reported observations thus far lack the rigour of a double blind, randomised trial of the two agents head to head, and until this is done, we should reserve judgement on

the generalisability of the result. It can be stated that the differences in observational studies may be artefactual, related to—for example—regression to the mean from a disease flare or a result of a placebo response.

In differences that have been recently reported in primary (first exposure) failure of efficacy, the difference may be related to specificity of the two antibody products (infliximab and adalimumab) for TNF α only, and the dual specificity of etanercept for TNF α and lymphotoxin α . I believe this to be a rare occurrence since TNF is the predominant cytokine overproduced in disease and is the molecule that best explains the shared common pathway of mechanism of action of all three agents.

The exposure of large populations of patients to anti-TNF drugs continuously for periods of up to five years has been reported since 2001 both as open label continuations of randomised controlled trials and observational studies from individual centres or national consortia. These studies demonstrate durability and safety of long term treatment with less than 10% attrition per year due to lack of efficacy or adverse events. The results are particularly noteworthy since populations studied with moderate to severe disease have previously failed on traditional disease modifying antirheumatic drugs (DMARDs).

Analyses of reports of serious adverse events to regulatory authorities by voluntary action of physicians and from systematic recording of national registries are becoming available. These confirm the hypothesis that patients on anti-TNF are more susceptible to infections, especially by intracellular organisms in areas with a high endemic load. Since this was expected from the known function of TNF α in host defence, the infections are likely based on mechanisms of action of all three drugs. It also seems likely that coadministration of other immunosuppressive drugs, such as methotrexate, that are used for treatment of severe disease is a contributory factor. The markedly reduced incidence of this in Spain following strict screening methods teaches us that this risk can be managed successfully, but probably not eliminated.

The increased incidence of B cell lymphoma in clinical trials of all anti-TNF agents have raised a concern of the possibility of a causal link. The issue is whether the increased incidence is simply reflecting the fact that patients with more severe RA are receiving anti-TNF drugs, and that this selection factor is reflecting the natural history of the disease in patients with severe RA, who are up to 28 times more likely to develop lymphoma. Reports of the analysis of the Swedish registry of anti-TNF treated patients versus controls at this meeting support that this may indeed be the case. If the lack of a causal link is confirmed, it will allay the anxiety of treating physicians and their patients.

From the perspective of understanding the mechanism of occurrence of lymphomas in RA, the report we heard at this meeting from Lars Klareskog, that the Epstein–Barr virus infection load of lymphomas in anti-TNF treated patients is not increased, and is similar to that of the usual RA associated lymphomas, is reassuring. It suggests that immunosuppression does not play a part in the pathogenesis of such lymphomas. Hence the B cell mutational stress over time imposed by chronic inflammation in severe disease could be the culprit causal link.

ANTI-TNF THERAPY PLUS METHOTREXATE IS MORE EFFECTIVE THAN ANTI-TNF OR METHOTREXATE MONOTHERAPY

A multicentre randomised placebo controlled clinical trial in patients established on DMARD methotrexate (MTX) published in 1998 demonstrated the improved clinical efficacy of infliximab as adjunctive therapy compared with

either infliximab alone or placebo (plus low dose MTX) alone. In the last year the TEMPO trial has shown that not only is clinical efficacy of combined etanercept greater than etanercept or MTX alone in achieving clinical efficacy, but that this combination is especially impressive in retarding, or even reversing, structural damage assessed by radiographs. Similar data from the PREMIER study, disclosed at the American College of Rheumatology last year, show that the same is true for the combination of adalimumab and MTX. The ATTRACT and ASPIRE trials similarly have shown greater control of structural damage by infliximab and MTX versus MTX plus placebo in established RA and MTX-naive patients with early RA. The conclusion we may draw is that for the treatment of established RA that is unresponsive to DMARDs (the usual clinical scenario), failure of treatment with “gold standard” MTX is most successfully treated by adjunctive therapy with an anti-TNF agent.

At last year’s targeted therapy meeting, Centocor presented an analysis of predictive factors favouring a good radiographically determined response in MTX failures in early RA in the ASPIRE trial. These included a high baseline C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), high baseline Sharp score, and a high swollen joint count. The Leeds group recently elaborated on the predictive criteria by demonstrating that failure to suppress CRP at 12 weeks with infliximab defined a non-responder population.

The molecular target modulated by MTX that adds value to anti-TNF therapy remains elusive. It could be a cytokine or a T cell mediated function. Suppression of induced neutralising anti-TNF antibodies has been observed with all three biologicals and provides insight into one possible mechanism. Other mechanisms may exist and would provide clues to better molecular target combinations than have been revealed by, for example, by a failure of combination of etanercept and IL-1Ra. Studies of other combinations of effective targeted therapies are not yet known, but, when explored, will be illuminating. Meanwhile, it is noteworthy that in RA patients not responding well enough to MTX, clinical trials show that MTX efficacy is potentiated not only by anti-TNF agents, but also by rituximab, abacept, and tocilizumab. Clearly MTX holds a valuable clue!

One of the unexpected lessons that emerged from a retrospective analysis performed by Joseph Smolen and colleagues of the ATTRACT trial is the attenuated progression of structural damage in patients treated with infliximab plus MTX, despite lack of reduction in clinical evaluation of inflammation. This is strikingly different from the observed correlation between clinical indices of inflammation and structural damage with MTX therapy in this study, which is the expected outcome, in keeping with conventional wisdom. These data suggest that there is a differential effect on mechanisms that mediate these two pathologies. In animal and human studies TNF α expression is consistently more marked at the pannus junction than elsewhere in the joint, and this geographical distribution might explain the differential effect, as might a differential effect on TNF mediated effects on osteoclast and fibroblast mediated structural damage, when compared with TNF mediated effects on cell recruitment into the joint.

The combination of anti-TNF agents with MTX has shown even more impressive efficacy in the early stages of RA than in established disease. In this setting, control of remission levels in studies from Emery and Breedveld’s groups using infliximab was observed in ~50% of patients. In these studies there is a clear indication that the combination for one year (Emery’s group) and six months (Breedveld’s group), induces remission, which can be sustained on MTX alone. Induction of remission encourages the hypothesis that prevention of progression of RA in the early stages might

offer a cost effective strategy in the management of this disabling disease. However, this management strategy needs to be evaluated in the light of the improved outcomes revealed in recently published clinical trials on combinations of standard drugs and higher doses of MTX than were used in clinical practice in the past.

HEALING AND REGENERATION: A KEY STEP IN FUTURE DEVELOPMENTS?

An unanswered question is the frequency of healing of erosive and destructive pathology. Sequential radiographs suggest this is possible in a significant proportion of patients on all anti-TNF drugs. Of course it will be important to know whether healing is truly associated with biomechanically competent functionality. Healing and regeneration of cartilage and bone is a phenomenon that has been well documented as a consequence of anti-TNF treatment in the Kollias TNF α transgenic mouse. The use of sophisticated magnetic resonance and ultrasound imaging, and functional assessment may provide us direct evidence of this outcome in man. If achievable, it will encourage the concept that the capacity to heal and regenerate resides in adult joints and is a normal attribute. It will suggest that inhibition of anabolic pathways of mesenchymal and haematopoietic cells by TNF is a significant negative component in the process of healing of damage. Agonists of pathways that promote bone and cartilage regeneration, for example involving the transforming growth factor β (TGF β) family, angiogenesis and notch pathways, may provide additional benefit and could be logical targets for dual targeting.

The cost of biologicals and safety issues continue to restrict widespread use and rationing of anti-TNF agents and

biologicals in general. New methods of production of biologicals are more likely to offer agents that are more cost effective than the current generation of anti-TNF drugs.

The emerging evidence of lack or loss of efficacy of anti-TNF agents in 30–50% of patients has highlighted the fact that there is a continuing unmet need. Future biologicals not only will need to be more cost effective but will also need to show anti-inflammatory and healing properties without immunosuppression and other adverse events. Uncoupling of these properties in favour of cost effective efficacy will be a difficult task to achieve. There can be no doubt that anti-TNF drugs provide a reference point from which to move forwards. The understanding of the mechanisms of action of TNF blockade that are being uncovered, and which I have not reviewed today, provides us with an overview of the big picture of loss of biological homeostasis in chronic rheumatic diseases. Environmental pressures that set in train the chronic immune-inflammatory cascade is revealing many key cells and molecules that interact in this complex ecosystem. The key to the future lies in the discovery of sensitive, reversible points in this mélange of dysfunctional networks.

It is a safe prediction that the annual targeted therapy meeting will continue as the most informative and educational meeting. It will be the forum at which news of these advances will be received. It will be a privilege to be among the participants when these advances occur.

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