Review

Current and new antitumor necrosis factor agents in perspective

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Introduction

Tumor necrosis factor (TNF) is a potent proinflammatory mediator. Experimental and clinical evidence indicates that TNF is present in high concentrations in the synovial tissue and fluid of patients with rheumatoid arthritis (RA); it has been shown to have a major role in the pathogenesis of rheumatic diseases and other immunologically mediated disorders [1–4]. TNF regulates the cytokine network, induces cellular recruitment to sites of inflammation, stimulates the synthesis and release of synovial tissue matrix metalloproteinases such as collagenase, downregulates proteoglycan synthesis in chondrocytes, inhibits osteoblastic collagen production, and upregulates osteoclastic activity [5,6].

Two proof-of-concept trials of anti-TNF agents, by Elliott and colleagues, were conducted with infliximab (Remicade®; Centocor, Inc., Malvern, PA, USA), a monoclonal anti-TNF antibody, in the early 1990s [7,8]. The first report describing the administration of anti-TNF antibodies for the management of human autoimmune disease came from an open-label infliximab (then designated cA2) phase I/II trial in 20 patients with active RA [7]. Patients received either two infusions of infliximab 10 mg/kg at study entry and at week 2, or four infusions of infliximab 5 mg/kg at study entry and at days 4, 8, and 12, for a total dose of 20 mg/kg in each group [7]. Clinical and laboratory assessments were performed at weeks 1, 2, 3, 4, 6, and 8, and the best overall responses were observed at week 6 [7]. At week 6 there were significant clinical improvements in the Ritchie Articular Index (from a median of 28 at baseline to a median of 6, $P<0.001$), in swollen joint count (from 18 to 5, $P<0.001$), in the duration of morning stiffness (from 180 to 5 minutes, $P<0.001$ by Mann–Whitney test, adjusted), and in pain scores (from 7.1 to 1.9 units, $P<0.001$, adjusted) [7]. Results at week 6 for the laboratory parameters showed significant decreases in the levels of serum C-reactive protein (from 39.5 to 8 mg/l, $P<0.001$) and also in those of serum amyloid A and interleukin-6 [7].

The earlier trial was followed by a multi-centre randomized trial that compared infliximab (given as a single infusion at low dose [1 mg/kg] or high dose [10 mg/kg]) with placebo in 73 patients with active RA [8]. The primary end point was the achievement at week 4 of a Paulus 20% response, the components of which include clinical (tender/swollen joint scores, duration of morning stiffness), observational (patient and physician assessments of disease severity), and laboratory (erythrocyte sedimentation rate) variables [8]. On the basis of an intent-to-treat analysis, a greater number of patients reached the primary end point with infliximab (11 of 25 in the low-dose group, $P=0.0083$; 19 of 24 in the high-dose group, $P<0.0001$) than with placebo (2 of 24) [8].

Shortly thereafter another anti-TNF agent, the soluble protein etanercept (Enbrel®; Immunex Corp, Seattle, WA, USA), was developed and introduced for use in patients with RA in 1998. Infliximab with concomitant methotrexate was licensed in 1999, and these two agents became the first biologic response modifiers approved by the Food and Drug Administration (FDA) for the management of RA [9–11]. Since this symposium, the FDA has approved adalimumab (Humira™; Abbott Laboratories, Abbott Park, IL, USA) for the treatment of patients with RA [12]. In 2000 a consensus panel of rheumatology experts emphasized that a hierarchy of disease-modifying antirheumatic drugs (DMARDs)/biologics exists and that biologics might be appropriate to use at any time during therapy depending upon disease and response; further, anti-TNF agents should not be used solely for advanced disease [13].

Unlike the conventional DMARDs, the TNF biologic response modifiers are genetically engineered (that is, developed by means of recombinant technology) and specifically target TNF; they therefore have an adverse event profile that in some respects is different from that seen with the DMARDs (for example, those related to hepatic, pulmonary, hematologic, and gastrointestinal

DMARDs = disease-modifying antirheumatic drugs; FDA = Food and Drug Administration; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

systems) [9,14,15]. Data from randomized clinical trials have not demonstrated an increased frequency of serious adverse events with the use of anti-TNF agents, although concerns about their short-term and long-term safety have been raised in postmarketing surveillance [16]. In spite of this, the anti-TNF agents have become widely used and have changed the practice of RA therapy. Infliximab and etanercept had been administered to more than 271,000 patients as of February 2002 (data on file; Centocor, Inc.) and to 121,000 patients by September 2001 (data on file; Immunex Corp). The administration of TNF antagonists has resulted in an inhibition of structural damage, rapid and substantial improvement in signs and symptoms, and improvement in physical function and quality of life for patients with RA.

The three anti-TNF agents have distinctly different pharmacokinetic and pharmacodynamic properties, including differences in chemical structure, receptor binding characteristics, serum half-lives, and routes of parenteral administration [17]. Although there have been no direct comparisons of these agents, sufficient clinical data have accumulated for investigators and clinicians to gauge the efficacy and safety of all three TNF antagonists and to assess the dosing methods and schedules.

On 27 October 2002, a panel of experts in rheumatology assembled in New Orleans, Louisiana, to debate these issues and place the new anti-TNF agents in perspective. The symposium was conducted in two segments. The first part dealt with the efficacy, safety, and route of administration of the three anti-TNF agents for the management of RA, and the second consisted of discussions pertaining to spondyloarthropathies (namely ankylosing spondylitis, psoriatic arthritis) for the then-available anti-TNF agents, infliximab and etanercept. This supplement represents the sum of the experts' efforts.

Competing interests

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References

1. Eigler A, Sinha B, Hartmann G, Endres S: **Taming TNF: strategies to restrain this proinflammatory cytokine.** *Immunol Today* 1997, **18:**487-492.
2. Punzi L, Calo L, Plebani M: **Clinical significance of cytokine determination in synovial fluid.** *Crit Rev Clin Lab Sci* 2002, **39:**63-88.
3. Feldmann M, Brennan FM, Maini RN: **Role of cytokines in rheumatoid arthritis.** *Annu Rev Immunol* 1996, **14:**397-440.
4. Feldmann M, Maini RN: **Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned?** *Annu Rev Immunol* 2001, **19:** 163-196.
5. Brennan FM, Maini RN, Feldmann M: **TNF alpha – a pivotal role in rheumatoid arthritis?** *Br J Rheumatol* 1992, **31:**293-298.
6. Maini RN, Feldmann M: **How does infliximab work in rheumatoid arthritis?** *Arthritis Res* 2002, **4(Suppl 2)**: S22-S28.
7. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, Brennan FM, Walker J, Bijl H, Ghrayeb J, Woody JN: **Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α.** *Arthritis Rheum* 1993, **36:** 1681-1690.
8. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H, Woody JN: **Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis.** *Lancet* 1994, **344:**1105-1110.
9. Lee DM, Weinblatt ME: **Rheumatoid arthritis.** *Lancet* 2001, **358:** 903-911.
10. Medical Economics Company Inc: **Prescribing information: Enbrel®.** In *Physicians' Desk Reference®.* Montvale, NJ; 2002:3504-3507.
11. Centocor, Inc.: **Remicade: Package insert, revised June 2002.** Malvern, PA; 2002.
12. Abbott Laboratories: **Humira: Package insert.** Abbott Park, IL; 2002.
13. Wolfe F, Cush JJ, O'Dell JR, Kavanaugh A, Kremer JM, Lane NE, Moreland LW, Paulus HE, Pincus T, Russell AS, Wilskie KR: **Consensus recommendations for the assessment and treatment of rheumatoid arthritis.** *J Rheumatol* 2001, **28:**1423-1430.
14. Kremer JM: **Rational use of new and existing disease-modifying agents in rheumatoid arthritis.** *Ann Intern Med* 2001, **134:** 695-706.
15. Geborek P, Crnkic M, Teleman A: **Tolerability using survival on drug as evaluation tool. Experience of etanercept, infliximab and lefluonomide in rheumatoid arthritis (RA) [abstract].** *Presented at the American College of Rheumatology 65th Annual Scientific Meeting/Association of Rheumatology Health Professionals 36th Annual Scientific Meeting; November 10–15, 2001; San Francisco, CA.*
16. American College of Rheumatology: **FDA advisory committee reviews safety of TNF inhibitors** [www.rheumatology.org/research/hotline/0901tnf.html]. Accessed 22 April 2002.
17. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, Wagner C: **Binding and functional comparisons of two types of tumor necrosis factor antagonists.** *J Pharmacol Exp Ther* 2002, **301:**418-426.

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