the tests in more correlated to the reference standard than the others, it will most likely perform better than the other tests. For example, if the reference standard included optic nerve head assessment at the slit lamp and one of the tests being evaluated involves the assessment of optic nerve head stereophotographs, its performance will likely be overestimated, as the appearance of the optic nerve head in photographs will be highly correlated to that at the slit lamp. This does not necessarily invalidate the study, but clinicians have to be aware of these issues so that they can evaluate the applicability of diagnostic accuracy estimates in the relevant population.

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REFERENCES

1 **Reus NJ**, de Graaf M, Lemij HG. Accuracy of GDx VCC, HRT I, and clinical assessment of stereoscopic optic nerve head photographs for diagnosing glaucoma. *Br J Ophthalmol* 2007;**91**:313–8.
2 **Panju AA**, Hemmelgarn BR, Guyatt GH, *et al*. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998;**280**:1256–63.
3 **Jaeschke R**, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *Jama* 1994;**271**:389–91.
4 **Lijmer JG**, Mol BW, Heisterkamp S, *et al*. Empirical evidence of design-related bias in studies of diagnostic tests. *Jama* 1999;**282**:1061–6.
5 **van der Schouw YT**, Verbeek AL, Ruijs SH. Guidelines for the assessment of new diagnostic tests. *Invest Radiol* 1995;**30**:334–40.
6 **Medeiros FA**, Zangwill LM, Bowd C, *et al*. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. *Am J Ophthalmol* 2005;**139**:1010–8.

Treatment of uveitis

Adalimumab in the therapy of uveitis in childhood

Ahmad M Mansour

''Adalimumab is more effective'' …?

Worldwide, around one million patients have been treated with tumour necrosis factor (TNF)-α antagonists (etanercept, infliximab or adalimumab) for rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease. Treatment results in substantial improvement in the signs and symptoms of arthritis (inhibition of progression of radiographic joint damage in psoriatic arthritis, resumption of growth in juvenile idiopathic arthritis (JIA) and attenuation of spinal inflammation in ankylosing spondylitis) as well as improved functional status and quality of life.[1] The use of TNF antagonists in adult uveitis has also been promising in small series.[2–4] Recently, TNF antagonists were also used in paediatric uveitis[5 6] and studies have shown the superiority of infliximab to etanercept in juvenile uveitis.[7] Vasquez-Kobian *et al*[5] released their results in October 2006 regarding the use of adalimumab in juvenile uveitis. Similarly in this issue, Biester *et al*[8] report that the use of adalimumab in refractory juvenile uveitis has good visual outcome (***see pages 319***). However, since the approval of TNF antagonists, concerns have been raised regarding their safety especially in children. We describe the differences between the three biologic therapies regarding modes of action, visual results, side effects and economic impact on health, and review preliminary evidence suggesting the potential superiority of adalimumab in JIA uveitis.

Adalimumab is a fully human immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to TNF and neutralises the biological activities of this cytokine by blocking its interaction with the p55 and p75 cell surface TNF receptors. Given the known role of TNF in uveitis, the efficacy and safety of adalimumab in the treatment of uveitis in JIA was analysed by Biester *et al*.[8] Chronic asymptomatic anterior uveitis occurs in 10–30% of patients with JIA, usually within 4 years of the onset of arthritis, and is associated with a high frequency of non-specific low-titre antinuclear antibodies. Long-term visual outcome in JIA-associated uveitis has been described as poor, with one third of patients developing substantial visual impairment and 10% becoming blind.[6 9] Most patients with JIA are already on non-steroidal anti-inflammatory drugs because of their arthritis and the drug of choice for polyarthritis is frequently methotrexate. According to several recent reports, low-dose oral methotrexate is effective in the treatment of chronic non-infective uveitis.[9] However, if more effective treatment is needed, systemic glucocorticosteroids and/or low-dose cyclosporine are added. In patients with refractory chronic uveitis, treatment with a TNF antagonist is indicated.[6]

The three TNF antagonists (etanercept, infliximab and adalimumab) had similar efficacy in rheumatoid arthritis, but that does not appear to be the case with uveitis, where infliximab is more effective than etanercept in both childhood[7] and adult uveitis.[4 10] Both adalimumab and infliximab were effective in reducing uveitis flares in patients with spondylarthropathy but etanercept was not.[11] Although infliximab was an effective short-term immunosuppressive agent with clear benefit, the rate of serious toxic effects was unexpectedly high in a prospective study.[2] Adalimumab was effective in controlling 80.8% of paediatric uveitis cases,[5] three cases of Behcet uveitis resistant to infliximab[3] and spondyloarthropathy-related uveitis.[11] Ocular response to adalimumab in JIA uveitis occurred within the first 2–6 weeks of therapy.[5] Arthritis response to adalimumab was much faster with 10 (22.2%) of 45 patients achieving a clinical response within 24 h of dosing.[12] In this issue, Biester *et al*[8] found retrospectively that adalimumab was well tolerated and decreased the relapse rate in JIA uveitis cases previously unresponsive to combined therapies (including infliximab), with minimal side effects (absence of anaphylactic reaction or infection).

To explain the therapeutic discrepancy between TNF-α antagonists, several hypotheses have been put forward relating to differences in molecular structure, mechanism of action, pharmacokinetics (kinetics, route and frequency of administration, type of TNF binding) and pharmacodynamics (apoptosis induction, TNF immunoprecipitation) (table 1).[1 13] Etanercept and infliximab have different binding characteristics, with infliximab and adalimumab binding to both soluble and membrane-bound TNF, while etanercept binds primarily to soluble TNF. These differences in binding may manifest as differing effects on complement activation and apoptosis. Etanercept and infliximab also have different pharmacokinetic profiles that may influence their activity. Because infliximab is administered as

Table 1 Biochemical and clinical profiles of anti-TNF agents[1 13]

Agent (company)	Mechanism of action	Administration (half life)	Status	Average dose (duration) varies with severity, disease and body weight	Adverse effect	Monitoring
Etanercept (Amgen Wyeth)	TNF-α inhibitor TNF receptor	SC twice weekly (4 days)	FDA approved for RA, JA, AS psoriasis, psoriatic arthritis	25 mg SC 2×/week (24 weeks) or 50 mg SC 2×/week (24 weeks) in adult; 0.4 mg/kg 2×/week in paediatric	Injection site reaction	CBC
Infliximab (Centocor)	TNF-α inhibitor chimeric antibody	IV infusion >120 min (9 days)	Phase III trials for psoriasis, FDA approved for RA, psoriatic arthritis, Crohn's disease	3 mg/kg (0, 2, 6 weeks) or 5 mg/kg (0, 2, 6 weeks)	Anaphylactic reactions; tuberculosis	Baseline PPD; liver enzymes
Adalimumab (Abbott Laboratories)	TNF-α inhibitor-human antibody	SC once weekly/ every other week (15 days)	FDA approved for RA phase III trials for psoriasis, psoriatic arthritis	80 mg week 0, 1 then 40 mg q week (12 weeks) or q 2 weeks in adult; 20–40 mg q 2 weeks in paediatric	Tuberculosis; injection site reaction	Baseline PPD; liver enzymes

AS, ankylosing spondylitis; CBC, complete blood count; FDA, Food and Drug Administration; IV, intravenous; JA, juvenile arthritis; PPD, purified protein derivative; q week, once weekly; q 2 weeks, once every 2 weeks; RA, rheumatoid arthritis; SC, subcutaneous.

bolus injections every 4–8 weeks, there is great variability in concentrations over time (high peaks separated by periods of low levels, with the high peaks possibly contributing to greater tissue penetration), whereas etanercept is administered subcutaneously twice weekly and adalimumab subcutaneously once every 2 weeks. Adalimumab therapy was generally well tolerated[1] and appeared to be less immunogenic than infliximab. The incidence of antibodies against infliximab increased from approximately 45% after the first infusion to 61% after the fifth infusion. Importantly, the duration of the clinical response was shortened in the presence of anti-infliximab antibodies. Concomitant methotrexate therapy was associated with a reduced incidence of antibody development. Twelve per cent of patients treated with adalimumab alone were antibody-positive compared to 1% of patients treated with adalimumab plus methotrexate.[14] Unlike infliximab, no demyelinating disorders or lupus-like syndromes occurred with adalimumab administration. Infliximab was associated with a higher risk than adalimumab of requiring intensification of immunosuppressive therapy than the other anti-TNF agents and a significant dose escalation over time. Analysis of rheumatic disease activity indicated a reduced therapeutic response to infliximab after the first 6 months of treatment, suggestive of acquired drug resistance.[15]

There is a risk of reactivation of granulomatous diseases with TNF antagonists, especially tuberculosis, and measures should be taken to detect and treat latent tuberculosis infections.[16] Preliminary data suggest that anti-TNF therapy may be safe in chronic hepatitis C. However, TNF antagonists have resulted in reactivation of chronic hepatitis B if not given concurrently with antiviral therapy. Solid tumours do not appear to be increased with anti-TNF therapy. Variable rates of increased lymphoma risk have been described with anti-TNF therapy compared with the general population, although no increased risk was found compared with a rheumatoid arthritis population. Trials with TNF antagonists in advanced heart failure have shown trends towards a worse prognosis, and TNF antagonists should therefore be avoided in this population. Rare cases of aplastic anaemia, pancytopenia and vasculitis have been described with anti-TNF therapy. Optic neuritis was reported in six cases (four cases with etanercept and two with adalimumab).[17 18]

Despite their clinical effectiveness, these agents are expensive and the annual cost of treatment ranges from US$12 000 to US$16 000. A recent study reported the mean direct costs of treating patients with TNF inhibitors to be almost three times higher (US$19 016) than treating those not receiving these agents (US$6164).[16] Costs to the patient and insurance/formulary coverage were perceived by rheumatologists as major barriers in prescribing TNF inhibitors.[16] Different routes of administration resulted in different coverage and reimbursement policies in the US and elsewhere. Medicare (and several private insurance companies around the world) covers infliximab, which is administered intravenously, while etanercept and adalimumab are administered subcutaneously and are not covered. In a national survey of practicing United States rheumatologists, adalimumab was perceived to be the least problematic drug, maybe because of its easy dosing schedule (40 mg every other week as compared to 25 mg twice a week for etanercept, and a loading dose at baseline, 2, 6 and every 8 weeks for infliximab) which might result in better outcomes in patient with rheumatoid arthritis.[16] A retrospective study of health plan costs related to rheumatoid arthritis revealed that etanercept was associated with lower drug and outpatient costs to the health plan than infliximab and adalimumab.[19] Compared with etanercept, infliximab was related to 55% higher post-index rheumatoid arthritis-related monthly total health care costs paid by the health plan, and adalimumab had 12% higher costs.

We should not forget that periocular long-acting depot corticosteroids remain one of the most clinically efficient cost-effective local therapies for adult and some childhood uveitis.[20] They can be administered without general anaesthesia in selected cooperative subjects after discussion with the parents and the patient. Unlike the situation in adults, we apply excess topical anaesthesia and use a wire eyelid retractor and forceps to hold Tenon's capsule to ensure immobilisation of the globe during injection. We need to be cautious about anti-TNF therapy in children (as the long-term effects are not known) and reserve it for non-responsive uveitis.

In conclusion, adalimumab has so far demonstrated some preliminary advantages over infliximab, including subcutaneous route of administration, no need for hospitalisation, dosage every 2 weeks, being less immunogenic and less expensive, and having a more a protracted therapeutic response in uveitis.[5 8] However, we need large long-term prospective randomised series with direct comparison between infliximab and adalimumab. As demonstrated by Biester *et al*,[8] the group of TNF inhibitors has enlarged our repertoire of effective treat-

ment modalities in uveitis, in addition to immunosuppressive drugs.

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REFERENCES

1 **Gordon KB**, Langley RG, Leonardi C, *et al*. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;**55**:598–606.
2 **Suhler EB**, Smith JR, Wertheim MS, *et al*. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol* 2005;**123**:903–12.
3 **Mushtaq B**, Saeed T, Situnayake RD, *et al*. Adalimumab for sight-threatening uveitis in Behcet's disease. *Eye*. Published Online First: 7 April 2006. doi: 10.1038/sj.eye.6702352.
4 **Galor A**, Perez VL, Hammel JP, *et al*. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology* 2006;**113**(12):2317–23.
5 **Vazquez-Cobian LB**, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. *J Pediatr* 2006;**149**:572–5.
6 **Kump LI**, Cervantes Castaneda RA, Androud SN, *et al*. Visual outcomes in children with juvenile idiopathic arthritis-associated uveitis. *Ophthalmology* 2006;**113**:1874–7.
7 **Saurenmann RK**, Levin AV, Rose JB, *et al*. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology* 2006;**45**:982–9.
8 **Biester S**, Deuter C, Michels H, *et al*. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;**91**:319–24.
9 **Kotaniemi K**, Savolainen A, Karma A, *et al*. Recent advances in uveitis of juvenile idiopathic arthritis. *Surv Ophthalmol* 2003;**48**:489–502.
10 **Gale S**, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine* 2006;**33**:231–7.
11 **Guignard S**, Gossec L, Salliot C, *et al*. Efficacy of tumor necrosis factor blockers in reducing uveitis flares in spondylarthropathy patients: a retrospective study. *Ann Rheum Dis* 2006;**65**:1631–4.
12 **Weisman MH**, Moreland LW, Furst DE, *et al*. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther* 2003;**25**:1700–21.
13 **Haraoui B**. Differentiating the efficacy of tumor necrosis factor inhibitors. *J Rheumatol Suppl* 2005;**74**:3–7.
14 **Anderson PJ**. Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005;**34**(5 Suppl 1):19–22.
15 **Nestorov I**. Clinical pharmacokinetics of TNF antagonists: how do they differ? *Semin Arthritis Rheum* 2005;**34**(5 Suppl 1):12–18.
16 **Kamal KM**, Madhavan SS, Hornsby JAA, *et al*. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. *Joint Bone Spine* 2006;**73**(6):718–24.
17 **Tauber T**, Turetz J, Barash J, *et al*. Optic neuritis associated with etanercept therapy for juvenile arthritis. *J AAPOS* 2006;**10**:26–9.
18 **Chung JH**, Van Stavern GP, Frohman LP, *et al*. Adalimumab-associated optic neuritis. *J Neurol Sci* 2006;**244**:133–6.
19 **Woolley JM**. Comparison of costs associated with the use of etanercept, infliximab, and adalimumab for the treatment of rheumatoid arthritis. *Manag Care Interface* 2006;**19**:47–53.
20 **Mansour AM**. Infliximab treatment of posterior uveitis. *Ophthalmology* 2004;**111**:197–8.

All skin cancers are not created equal

Jeffrey A Nerad

The diagnosis of squamous cell carcinoma deserves a high degree of respect and care in confirming complete excision.

Gokmen Soysal and Markoc,[1] in their paper titled, Invasive squamous cell carcinoma of the Eyelids and Periorbital Region, remind us of the serious nature of squamous cell carcinoma (SCC) and its potential for devastating consequences (***see page 325***). Early diagnosis remains an important feature of treatment. Aggressive surgical excision, especially when the lesion is small, offers the highest cure rate. Preventative measures and newer treatment modalities may offer some prophylaxis.

How serious is cutaneous SCC? 60 000 new cases of skin cancer are diagnosed each year in the UK.[2] Over one million new cases of skin cancer are diagnosed each year in the United States.[3] These include basal cell carcinoma (BCC), SCC, melanoma and sebaceous cell carcinoma. BCC and SCC, both having a similar etiologic relationship to actinic damage, are collectively, referred to as nonmelanotic skin cancers (NMCC) and represent the most common form of cancer today. UV exposure has been shown to be a risk factor for cutaneous melanoma also. It is estimated that 50% of adults will have a NMCC by age 65.[4] BCC represent more than 90% of these tumors. SCC, however, is a much more aggressive and potentially invasive neoplasm.

Gokmen Soysal and Markoc report on 76 patients with periorbital SCC. Orbital invasion was present in a large percentage of patients: 33/76 patients (43.4%). Of these 7/33 had paranasal sinus extension as well. Intracranial involvement was present in 1 patient. Lymph node involvement was seen in 6.6% of patients. Other recent reports show high morbidity, although not as high as shown by Gokmen Soysal and Markoc. Donaldson *et al*[5] reported on 50 cases of SCC of the eyelids. Orbital invasion was found in three patients (6%) and treated with exenteration in two. The third patient died as a result of local extension of the tumor. No distant or regional metastases were identified over a 31 month follow up period. Faustina *et al*[6] reported that 7/111 (6.3%) required orbital exenteration. 27 (24.3%) eventually had regional spread and 6.2% had distant metastases. Although the exact percentage and pattern of local spread varies among these individual studies, likely due to referral pattern, and perhaps follow up length, it is clear that SCC is associated with a high level of morbidity and sometimes mortality.

What histopathologic characteristics suggest an aggressive nature of these tumors? The manuscript illustrates three characteristics known to be associated with aggressive behavior: subtype, perineural invasion (PNI), and associated inflammation. SCC is categorised histopathologically by subtype ranging from well differentiated to poorly differentiated. In the study by Gokmen Soysal and Markoc, 11.9% of tumors considered poorly differentiated, and all of these demonstrated orbital extension. In the study by Malhotra,[7] 38% of recurrent tumors were either moderately or poorly differentiated. Perineural invasion (PNI) is associated with the higher morbidity of SCC. Gokmen Soysal and Markoc had a high rate of PNI (23.8%), perhaps consistent with the high percentage of patients with orbital invasion (43.4%). Bowyer *et al*[8] described the management of perineural spread in 17 patients with SCC. Numbness and pain were the most common symptoms, whereas ophthalmoplegia, ptosis and facial nerve palsy were the most common signs. Six of 17 had recurrent tumor and the disease progression resulted in death in four of these six patients. Four of 50 patients in Donaldson's study had PNI. Faustina's study did not discuss PNI. Of the 79 patients in Malhotra's study three had PNI and two of the three were recurrent