Successful treatment of inflammatory knee osteoarthritis with tumour necrosis factor blockade

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Increasing evidence indicates that tumour necrosis factor (TNF) has an important role not only in inflammatory arthritis but also in degenerative joint disease.[1–3] TNF controls the homoeostasis of matrix synthesis and matrix degeneration in articular cartilage in concert with other cytokines, such as interleukin 1 (IL1), transforming growth factor β, or insulin-like growth factor 1. Overproduction of TNF and IL1 skews the balance towards matrix degradation, at least in part by virtue of induction of nitric oxide synthesis and subsequent metalloproteinase production. In osteoarthritis (OA), increased TNF production by activated synoviocytes and articular chondrocytes together with increased p55 TNF receptor expression on chondrocytes imply the contribution of TNF mediated matrix degradation to disease pathogenesis.[1 4 5] As inhibition of TNF has been shown to suppress nitric oxide production in human cartilage,[6] the hypothesis can be formulated that anti-TNF therapy might be a promising strategy for the treatment of OA.[7–9]

A common clinical feature of OA is bone marrow oedema, which can be detected and quantified by magnetic resonance imaging (MRI). Prevalence and size of bone marrow oedema are related to the degree of cartilage damage[10] and to some extent to the severity of pain perceived by the patient.[11 12]

Here, we report the case of a 68 year old male patient with bilateral OA of the knees. Shortly after the start of symptoms in May 2005, he received high doses of non-steroidal anti-inflammatory drugs, without major clinical benefit. Pain increased with time and not only impaired daily activities but also severely disturbed the patient at night. MRI imaging in August 2005 showed severe damage of the articular cartilage in both knees, associated with substantial bone marrow oedema. Additionally, there were signs of arthritic activation with a small synovial effusion and marked synovitis (fig 1).

Self medication by the patient—a professor of medicine and specialist in rheumatology—with steroid doses of up to 50 mg/day—led to a prompt relief of symptoms; however, these immediately recurred when the drug was stopped. Given the potential role of TNF in OA, an experimental treatment with the fully human TNF antibody, adalimumab, was started. The patient was treated with the equivalent dose of the antibody recommended for the treatment of rheumatoid arthritis (40 mg subcutaneously every other week). After the second dose, nocturnal pain in the patient's knees completely resolved. Walking, which had been fairly impossible at the beginning of the treatment, was now feasible up to a distance of 1000 m, with only marginal pain. Subsequently, dosing of the TNF inhibitor was adapted to the patient's needs, resulting in treatment intervals of 3–6 weeks. With this treatment regimen and addition of a low dose COX 2-inhibitor, the patient is now almost free of symptoms. Figure 1 shows an MRI analysis of the patient's right knee before and 6 months after the start of adalimumab therapy. Synovial effusion and synovitis are visibly decreased, while bone marrow oedema has nearly vanished.

This is the first report of a successful treatment of debilitating pain resulting from severe OA with a monoclonal antibody to TNF. The value of anti-TNF therapy as an option in severe OA needs to be established in larger controlled trials.

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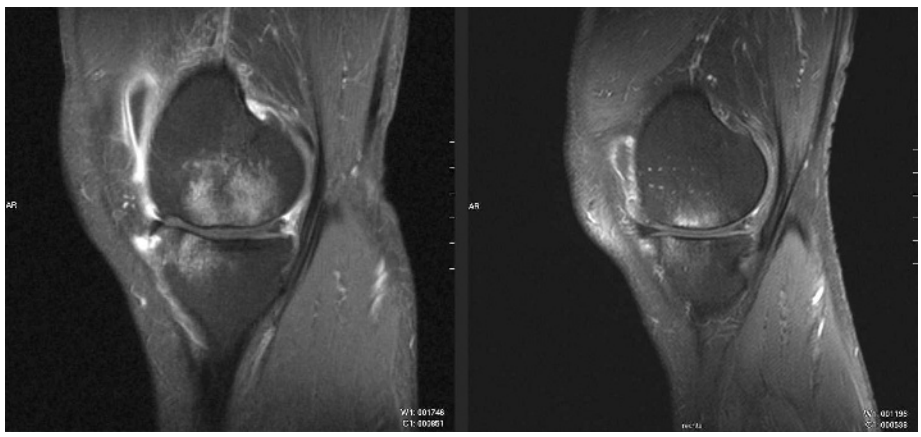

Figure 1 Contrast enhanced T_1 weighted MRI scan of the patient's right knee before (left) and 6 months after initiation of adalimumab therapy (right).

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Association analysis of the interleukin 17 genes IL17A and IL17F as potential osteoarthritis susceptibility loci

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Primary osteoarthritis (OA) has a major genetic component that is transmitted in a complex, non-mendelian manner. We previously conducted a genome-wide linkage scan on OA affected sibling-pair families and identified several genomic regions potentially harbouring OA risk loci. The strongest evidence was obtained on chromosome 6p12.3–q13, with a multipoint logarithm of the odds score of 4.0.[1] This linkage was restricted to the 146 families in our cohort that contained female sibling-pairs concordant for hip OA. A subsequent high density microsatellite linkage scan of the interval provided further strong evidence for linkage as well as evidence of association with several markers, including D6S1956.[2] This marker is located less than 200 kb distal of the interleukin 17 (IL17) genes, IL17A and IL17F.

IL17 was originally identified as a product of CD4+ memory T cells, with subsequent studies demonstrating secretion by CD8+ cells.[3 4] IL17 is an inducer of several cytokines, including tumour necrosis factor α, IL1, IL6, and RANKL. A number of investigations have demonstrated a role for IL17 in the aetiology and progression of rheumatoid arthritis; the cytokine is expressed by rheumatoid synovium and can induce inflammation and osteoclastic bone resorption.[5 6] Other studies have shown a widespread pattern of tissue expression of IL17 and its receptors, including expression in articular cartilage.[3 4] The ability of IL17 to induce catabolic cytokines, nitric oxide, and collagenases in cartilage and in chondrocytes has also been demonstrated, implying a role in cartilage biology.[7–10]

These biological data, along with our previous genetic results, prompted us to consider IL17A and IL17F as candidates for the strong OA susceptibility that we had mapped to chromosome 6. To maximise our chances of detecting a genetic association we focused on the probands from the 146 female-hip OA families that had provided us with the original linkage. These probands were ascertained through signs and symptoms of OA to have sufficiently severe disease to require hip joint replacement surgery. The radiological stage of the disease was a Kellgren and Lawrence grade of 2 or more. Inflammatory arthritis was excluded as was post-traumatic arthritis, post-septic arthritis, skeletal dysplasia, and developmental dysplasia. Our controls comprised 215 women with no signs or symptoms of arthritis or joint disease. All probands and all controls were white, from the UK, and aged 55 or over.

The exons, the intron-exon boundaries, and the untranslated regions of IL17A and IL17F were screened for common DNA variants by the direct sequencing of 48 women and by searching genome databases. We identified 10 single nucleotide polymorphisms (SNPs), five in IL17A and five in IL17F (table 1). The SNPs were genotyped by polymerase chain reaction restriction enzyme analysis and were in Hardy-Weinberg equilibrium. Two of the IL17A SNPs (rs8193037 and rs3819025) and two of the IL17F SNPs (rs1953325 and rs763780) had low allele frequencies (<0.05) and their genotyping was therefore not completed. Of the six remaining SNPs, two were non-synonymous (rs11465553 and

Table 1 IL17A and IL17F SNPs

Gene	SNP location*	Nucleotide change M→m†	Amino acid substitution	dbSNP accession number‡	Allele frequency§ (number) Probands	Controls	p Value
IL17A	Upstream	G→A	–	rs8193037	Not determined	0.01 (1/91)	–
IL17A	Intron 1	G→A	–	rs3819025	Not determined	0.03 (6/178)	–
IL17A	Exon 3/3′UTR	G→A	–	rs7747909	0.17 (48/230)	0.22 (95/331)	0.14
IL17A	Exon 3/3′UTR	C→T	–	rs1974226	0.19 (53/231)	0.19 (79/337)	0.99
IL17A	Exon 3/3′UTR	C→T	–	rs3748067	0.10 (28/260)	0.08 (35/389)	0.59
IL17F	Exon 3/3′UTR	T→G	–	rs1953325	Not determined	0.03 (6/174)	–
IL17F	Exon 3	A→G	His161Arg	rs763780	Not determined	0.03 (5/175)	–
IL17F	Exon 3	G→A	Val155Ile	rs11465553	0.04 (11/273)	0.06 (27/401)	0.22
IL17F	Exon 3	A→G	Glu126Gly	rs2397084	0.12 (34/252)	0.12 (52/374)	0.99
IL17F	Intron 1	G→A	–	rs11465551	0.07 (19/269)	0.07 (29/389)	0.98

*SNPs are listed in their physical order, from 6p-telomere to centromere; †M = major, common allele in controls; m = minor, less common allele in controls; ‡http://www.ncbi.nlm.nih.gov/SNP, accessed 27 December 2005; §frequency of the minor allele.