many open-label studies. About one-half of the patients achieve a ≥50% reduction in the BASDAI. The response tends to be stable over time, and partial or full remissions are common. Predictors of the best responses include younger age, shorter disease duration, higher baseline inflammatory markers, and lower baseline functional disability. Nonetheless, some patients with long-standing disease and even spinal ankylosis can obtain significant benefit. Increased bone mineral density is found as early as 24 weeks after onset of therapy. There is evidence that anti-TNF therapy does not prevent syndesmophyte formation, although this may apply mainly during the early years of therapy. A mechanism for this has been proposed based on the observation that TNF-α inhibits new bone formation by upregulating DKK-1, a negative regulator of the wingless (Wnt) signaling pathway that promotes osteoblast activity. Serum DKK-1 levels are inappropriately low in AS patients and are also suppressed by anti-TNF therapy.

Infliximab is given intravenously, 3–5 mg/kg body weight, and then repeated 2 weeks later, again 6 weeks later, and then at 8-week intervals. Etanercept is given by subcutaneous injection, 50 mg once weekly. Adalimumab is given by subcutaneous injection, 40 mg biweekly. Golimumab is given by subcutaneous injection, 50 or 100 mg every 4 weeks. Certolizumab pegol is given by subcutaneous injection, 400 mg every 4 weeks.

Although these potent immunosuppressive agents have thus far been relatively safe, patients are at increased risk for serious infections, including disseminated tuberculosis. Hypersensitivity infusion or injection site reactions are not uncommon. Cases of anti-TNF-induced psoriasis have been increasingly recognized. Rare cases of systemic lupus erythematosus–related disease have been reported, as have hematologic disorders such as pancytopenia, demyelinating disorders, exacerbation of congestive heart failure, and severe liver disease. The overall incidence of malignancy does not appear to be increased in AS patients treated with anti-TNF therapy, but isolated cases of hematologic malignancy have occurred shortly after the start of treatment.

Because of the expense, potentially serious side effects, and unknown long-term effects of these agents, their use should be restricted to patients with a definite diagnosis and active disease (BASDAI ≥4 out of 10 and expert opinion) that is inadequately responsive to therapy with at least two different NSAIDs. Before initiation of anti-TNF therapy, all patients should be tested for tuberculin (TB) reactivity, and reactors (≥5 mm on PPD testing or a positive quantiferon test) should be treated with anti-TB agents. Contraindications include active infection or high risk of infection; malignancy or premalignancy; and history of systemic lupus erythematosus, multiple sclerosis, or related autoimmunity. Pregnancy and breast-feeding are relative contraindications. Continuation beyond 12 weeks of therapy requires either a 50% reduction in BASDAI or absolute reduction of ≥2 out of 10, and favorable expert opinion. Switching to a second anti-TNF agent may be effective, especially if there was a response to the first that was lost rather than primary failure. Sulfasalazine, in doses of 2–3 g/d, has been shown to be of modest benefit, primarily for peripheral arthritis. A therapeutic trial of this agent should precede any use of anti-TNF agents in patients with predominantly peripheral arthritis. Methotrexate, although widely used, has not been shown to be of benefit in AS, nor has any therapeutic role for gold or oral glucocorticoids been documented. Potential benefit in AS has been reported for thalidomide, 200 mg/d, perhaps acting through inhibition of TNF-α.

Ustekinumab (anti-IL-12/23) and secukinumab (anti-IL-17) monoclonal antibodies have shown promising efficacy in clinical trials, but have not yet been approved for use in AS.

The most common indication for surgery in patients with AS is severe hip joint arthritis, the pain and stiffness of which are usually dramatically relieved by total hip arthroplasty. Rare patients may benefit from surgical correction of extreme flexion deformities of the spine or of atlantoaxial subluxation.

Attacks of uveitis are usually managed effectively with local glucocorticoid administration in conjunction with mydriatic agents, although systemic glucocorticoids, immunosuppressive drugs, or anti-TNF therapy may be required. TNF inhibitors reduce the frequency of attacks of uveitis in patients with AS, although cases of new or recurrent uveitis after use of a TNF inhibitor have been observed, especially with etanercept.

Coexistent cardiac disease may require pacemaker implantation and/or aortic valve replacement. Management of axial osteoporosis is at present similar to that used for primary osteoporosis, since data specific for AS are not available.

REACTIVE ARTHRITIS

Reactive arthritis (ReA) refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. In recent years, the term has been used primarily to refer to SpA following enteric or urogenital infections.

Other forms of reactive and infection-related arthritis not associated with B27 and showing a spectrum of clinical features different from SpA, such as Lyme disease and rheumatic fever, are discussed in Chaps. 210 and 381.

HISTORIC BACKGROUND

The association of acute arthritis with episodes of diarrhea or urethritis has been recognized for centuries. A large number of cases during World Wars I and II focused attention on the triad of arthritis, urethritis, and conjunctivitis, often with additional mucocutaneous lesions, which became widely known by eponyms that are now of historic interest only.

The identification of bacterial species capable of triggering the clinical syndrome and the finding that many patients possess the B27 antigen led to the unifying concept of ReA as a clinical syndrome triggered by specific etiologic agents in a genetically susceptible host. A similar spectrum of clinical manifestations can be triggered by enteric infection with any of several *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter* species; by genital infection with *Chlamydia trachomatis*; and by other agents as well. The triad of arthritis, urethritis, and conjunctivitis represents a small part of the spectrum of the clinical manifestations of ReA and only a minority of patients present with this "classic triad" of symptoms. Although emerging data suggest that asymptomatic *Chlamydia trachomatis* infections might trigger ReA, for the purposes of this chapter, the use of the term *ReA* will be restricted to those cases of SpA in which there is at least presumptive evidence for a related symptomatic antecedent infection. Patients with clinical features of ReA who lack evidence of an antecedent infection will be considered to have *undifferentiated spondyloarthritis*, discussed below.

EPIDEMIOLOGY

Initial reports may have overestimated the association of ReA with HLA-B27, since 60–85% of patients who developed ReA triggered by *Shigella*, *Yersinia*, or *Chlamydia* were B27-positive. However, other studies demonstrated a lower prevalence of B27 in ReA triggered by *Salmonella*, with one study suggesting no association in *Campylobacter*-induced ReA. Several more recent community-based or common-source epidemic studies demonstrated that the prevalence of B27 in ReA was below 50%. The most common age range is 18–40 years, but ReA can occur rarely in children and occasionally in older adults.

The attack rate of postenteric ReA generally ranges from 1% to about 30% depending on the study and causative organism, whereas the attack rate of postchlamydial ReA is about 4–8%. The gender ratio in ReA following enteric infection is nearly 1:1, whereas venereally acquired ReA occurs mainly in men. The overall prevalence and incidence of ReA are difficult to assess because of the lack of validated diagnostic criteria, variable prevalence and arthritogenic potential of the triggering infectious agents, and inconstant genetic susceptibility factors in different populations. In Scandinavia, an annual incidence of 10–28:100,000 has been reported. The spondyloarthritides were formerly almost unknown in sub-Saharan Africa. However, ReA and other peripheral SpAs have now become the most common rheumatic diseases in Africans in the wake of the AIDS epidemic, without association to B27, which is very rare in these populations. ReA is often the first manifestation of HIV infection and often remits with disease progression. In contrast,