Available online http://arthritis-research.com/content/4/S3/S025

Supplement Review

Therapy of systemic lupus erythematosus: a look into the future

Josef S Smolen

Department of Rheumatology, Internal Medicine III, Vienna General Hospital, University of Vienna, and 2nd Department of Medicine, Lainz Hospital, Vienna, Austria

Correspondence: Josef S Smolen, MD, Department of Rheumatology, Internal Medicine III, Vienna General Hospital, University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Tel: +43 1 40400 4300; fax: +43 1 40400 4331; e-mail:smj@2me.khl.magwien.gv.at

Received: 19 March 2002
Accepted: 23 March 2002
Published: 9 May 2002

Arthritis Res 2002, **4 (suppl 3)**:S25-S30

© 2002 BioMed Central Ltd

(Print ISSN 1465-9905; Online ISSN 1465-9913)

This manuscript is dedicated to Professor Tiny Maini in admiration of his grand mind and great work, in thankful appreciation of the numerous hours of our scientific debates, discussions on the future of rheumatology, and great personal enjoyment over the past 15 years, and with sincere gratitude for his support, guidance, and friendship over so many years

Chapter summary

The prognosis for patients with systemic lupus erythematosus has greatly improved over the past two decades. However, therapies that are more effective and that have fewer sequelae are needed to rescue patients from organ failure and further reduce mortality. Research under way, including that into induction of tolerance to self-antigens, prevention of the consequences of pathogenic autoantibody production, interference with the cytokine network and signal transduction, the identification and treatment of any infectious triggers, and stem cell therapy, offers hope of improved remedies or even of cure. Given the fact that a number of biological therapies for rheumatologic disease are already in use or are in the development stage, such progress may come soon.

Keywords: systemic lupus erythematosus, therapy

Introduction

The prognosis of patients with systemic lupus erythematosus (SLE) has improved significantly over the past two decades [1]. Earlier diagnosis on the basis of better awareness, description of new autoantibody specificities, and improvement of serological techniques may have supported this development. However, the introduction of pulse cyclophosphamide therapy for lupus nephritis [2] as well as advances in hemodialysis techniques were pivotal for this improvement, since it was irreversible renal failure and its consequences that previously had a high impact on mortality [3]. Nevertheless, almost 10% of SLE patients still die within the first 5 years of their disease and their mean life expectancy is significantly shorter than in the general population, due partly to relentlessly progressive lupus in some patients and partly to sequelae of treatment, particularly those of cytotoxic agents and glucocorticoids [4,5]. This situation calls for the search for new therapeutic strategies with higher efficacy and lesser comorbidity.

SLE is the prototype non-organ-specific autoimmune disease. A multisystem disorder, it destroys cells and organs by means of autoantibodies and immune complexes. The mechanisms underlying the hyper-reactivity and autoreactivity of the immune system in SLE are unknown. A setting of genetic susceptibility involving multiple genes [6] in conjunction with environmental triggers constitutes the hypothetical etiopathogenic background. As long as the

A glossary of specialist terms used in this chapter appears at the end of the text section.

triggers of the disease are unknown, novel therapeutic approaches must be aimed mainly at interference with the generation of autoantibodies and immune complexes or with their consequences, namely cell destruction and inflammation. In this review, some of the many potential future therapeutic approaches are discussed. Further information is included in a recent textbook chapter [7].

Is there a potential for causative treatment?

The role of infectious triggers of autoimmune diseases has been debated for decades. The earliest evidence pointing to such associations stems from acute rheumatic fever induced by streptococcal infections and the subsequent generation of antistreptococcal antibodies, which cross-react with cardiac tissue and lead to rheumatic heart disease in susceptible individuals [8]. Type I diabetes has been often linked to Coxsackie virus infections [9]; some forms of vasculitis appear to be a consequence of infection with hepatitis B or C virus [10]; and peptide sequences of a variety of SLE-related autoantigens are homologous to sequences of various viral proteins [11–14]. In fact, a peptide of the Sm protein, which can elicit a variety of autoantibodies and experimental lupus in an immunized animal, has homologies with a protein present on Epstein–Barr virus (EBV) [15,16].

In contrast to the earlier, unsupported hypotheses, there is at least some recent important epidemiological evidence that SLE may be associated with EBV infection [16]. EBV is a common infection worldwide. In the African regions, EBV infection is commonly associated with a variety of malignancies [17]. In these regions, SLE is rare [18]. On the other hand, in the industrialized world, people of African origin have a high risk of developing SLE [18], while EBV-associated malignancies are rare in those regions. Thus, it is conceivable that under different environmental circumstances EBV may induce different diseases or be, at least, a cofactor in the pathogenesis of different disorders, one of them SLE. Importantly, as EBV is one cause of lymphomas in the industrialized world [17] and is usually contracted during adolescence, one wonders if the design of a vaccine protecting against EBV infection and given in early childhood would reduce the risk not only of such malignancies, but also of SLE.

Induction of tolerance

Autoimmune diseases are often considered to be a consequence of lost tolerance to self-antigens. Whether this is truly the case or there are other pathways responsible for the evolution of a pathogenic autoimmune response, induction of unresponsiveness and reversal of the respective immune response might constitute an interesting and successful therapeutic approach.

Given that some of the presumably most pathogenic types of autoantibodies in SLE are directed to dsDNA, downmodulation of their production is one important therapeutic aim. In experimental animals, a compound containing four oligonucleotides on a triethylene glycol backbone (LJP 394) is capable of downmodulating anti-dsDNA production, presumably by cross-linking the specific antigen receptor on the surface of the B cell. This approach led to amelioration of disease and higher survival in mice with lupus [19]. Anti-dsDNA was also reduced in patients with SLE who were treated with LJP 394 [20]. Phase II/III randomized controlled trials are now under way.

In patients with autoimmune diseases, autoantibodies are usually of the IgG class and have hypermutated V region genes in comparison with the germ line. This clearly suggests the involvement of T-cell help. In fact, T cells incubated with nucleosomes or histones in both experimental and human SLE support the production of anti-dsDNA by B cells [21,22]. Since autoimmunity directed towards histone H1 appears to be of pivotal importance in SLE [23], induction of tolerance to nucleosomal antigens may be an interesting approach; it has already been successfully applied in experimental models [24]. Moreover, activation of 'suppressor' T cells, which more than two decades ago were found to be defective in SLE [25] and have conceptually re-emerged more recently as 'regulatory' T cells [26], may be an interesting new therapeutic approach for the induction of unresponsiveness. Moreover, since interaction of CTLA-4 with its ligand CD80/86 interrupts the costimulatory pathways needed to activate T cells [27], application of a CTLA-4–IgG fusion protein may interfere with the immunologic processes involved in disease induction in mice and man [28,29] and lead to tolerance. Similar effects may be seen with antibodies to CD80/86 (B7.1 and 2) [30].

Tolerance may also be achieved by active immunization with tolerizing peptides and a reduction of autoantibody production has been observed experimentally when peptides from anti-dsDNA antibodies were used [31].

Prevention of the consequences of pathogenic autoantibody production

The mere presence of autoantibodies is not necessarily associated with disease. On the one hand, nonpathogenic autoimmunity is part of our 'normal' immunologic repertoire [32]; on the other hand, the pathogenicity of autoantibodies and the consequent immune complexes is mostly brought about by the activation of complement and the interaction with cell-membrane-bound Fc receptors. Thus, interference with the complement pathways, as in knockout mice or when specific antibodies are used, can prevent or ameliorate lupus [33,34]. Soluble complement receptors may also be beneficial [35]. Likewise, interference with the IgG Fcγ receptor (FcγR) interaction, as in FcγR I/III knockout mice or when anti-CD16 antibodies are used, can prevent the evolution of clinical manifestations of the disease [36,37]. On the other hand, activation of

inhibitory FcγRs which contain an immunoreceptor tyrosine inhibitory motif (ITIM), in contrast with the immunoreceptor tyrosine activation motif (ITAM) of other FcγRs [38], may downmodulate B-cell function when co-cross-linked with the B cell's antigen receptor. Such FcγR-mediated inhibition of B-cell activity may not only be induced by immune complexes that carry an antigen binding to the surface immunoglobulin of the B cell while the immunoglobulin moiety of the immune complex engages the FcγRIIb, but also by intravenous immunoglobulin [39]. There are reports of the efficacy of intravenous immunoglobulin in SLE [40], although further confirmation is awaited. The importance of FcγRs as potential therapeutic targets is also supported by reports on genetic linkage of SLE with a region on chromosome 1 that encodes the FcγRs [41].

The interventions discussed above were all directed at the consequences of immune complex production. However, considering autoantibody production, pathogenicity may also be prevented by interfering with autoantibody binding to the (auto)antigen or by eliminating the already bound autoantigen. The latter approach was not blessed with clinical efficacy, since the application of recombinant DNase, aiming at eliminating DNA from the respective immune complexes, had no clinical effects [42]. In contrast, the application of heparin, which prevents the binding of circulating charged nucleosomal antigens to the glomerular basement membrane, prevented the occurrence of nephritis in experimental lupus and possibly should constitute an adjunctive therapy in patients with lupus nephritis [43]. Another interesting means is to displace the antigen in the pathogenic immune complex with cross-reactive peptides. In one study, such an approach using peptides containing D-amino acids prevented glomerular deposition [44].

Interference with the cytokine network and signal transduction

Although the debate whether SLE is primarily a Th1- or a Th2-mediated disease is still unresolved, cytokines appear to play important roles both in human and murine lupus. Not only has IFN-γ been found to be highly increased in sera of patients with lupus [45], but therapy with this cytokine has led to activation and induction of SLE [46,47]. The value of IFN-γ as a therapeutic target is supported by the fact that IFN-γ knockout lupus-prone mice do not develop the disease; moreover, treatment of experimental SLE with IFN-γ receptors inhibits lupus nephritis [48–51]. All these notions are further supported by the observation of an amelioration of experimental lupus by the prototypic Th2 cytokine IL-4 [52].

While the lymphokines mentioned above play important roles in the generation of the primary immune response and its skewing towards specific reactivity patterns [53], the proinflammatory cytokines are significantly involved in tissue destruction. The central proinflammatory cytokines, tumor necrosis factor (TNF)-α and IL-1, are increased in SLE and can both be activated by immune complexes [54–56]. Moreover, we have recently observed significant amounts of TNF-α by immunohistochemistry in renal biopsies from patients with lupus nephritis (manuscript in preparation). Nevertheless, the role of TNF-α is currently under intensive discussion. On the one hand, in experimental animals, TNF can induce nephritis and TNF-α deficiency ameliorates nephritis [57,58]; on the other hand, injection of TNF-α can ameliorate murine SLE under certain circumstances [59]. This latter observation in conjunction with an occasional appearance of a lupus-like syndrome in patients with rheumatoid arthritis (RA) who are treated with TNF blockers [60] has led to the suggestion that TNF may be protective in lupus and that inhibition of TNF may therefore be potentially detrimental. However, not only are these events rare and, as of now, no more commonly observed than similar drug-induced lupus syndromes during many other therapies used for RA [61,62], but also the anti-dsDNA autoantibodies observed among patients treated with TNF blocker are not consistently observed and are usually of the IgM rather than a pathogenic IgG isotype [63,64].

To account for all these findings, my colleagues and I have proposed that TNF may play a dual role in SLE. This cytokine could well interfere with the regulation of the immune response and lead to an increase of autoantibody production; however, it may also have a critical role in the final pathway of SLE disease, namely immunologically induced and inflammation-induced tissue destruction. Thus, inhibition of TNF-α may, in fact, be a highly valuable tool in patients with active SLE, while inhibition of a potential autoantibody-enhancing activity could be achieved by concomitant immunosuppressive agents. The rapid interference of TNF blockers with the inflammatory response [65] suggests that they may be very beneficial for patients with active lupus nephritis and possibly other SLE manifestations [66,67]. Support for the efficacy and safety of TNF blockade in connective tissue disease stems from observations in patients with RA/SLE overlap (D Furst, personal communication) and individual cases of patients with mixed connective tissue disease ([68] and unpublished observations). My colleagues and I are currently embarking on a small clinical trial with Ethical Committee approval to address the potential of TNF blockade to ameliorate SLE.

Targeting signal transduction pathways

Proinflammatory cytokines and lymphokines mediate their effects by activating transcription factors via diverse signal transduction mechanisms induced after receptor ligation. Among the most important pathways are those involving mitogen-activated protein kinases (MAPKs) and nuclear

factor (NF)-κB as well as the Janus kinases (JAKs). Interference with these pathways can ameliorate inflammatory diseases. One compound already approved for RA, leflunomide, interferes with NFκB activation [69] and also has some beneficial effects on mild SLE [70,71]. Many other drugs are currently in development and may have a potential as future therapeutic agents [72,73].

Stem cell therapy

The use of myeloablative cytotoxic therapy to combat the immunoinflammatory insult, with subsequent stem cell rescue to replenish the hematopoietic system and reconstitute the immune system, may be an attractive way of treating aggressive forms of SLE. Autologous stem cell therapy has been performed in small series of patients in recent years with some success [74], and we ourselves also had successful results in relentlessly progressive, life-threatening SLE [75].

Conclusion

In summary, rescue from organ failure and survival of patients with SLE need to be further improved. Advances in immunology and molecular biology have provided new therapeutic targets and new tools for potential treatment success. It will be important to study such new therapies using thoroughly designed protocols [76], but clearly there is hope for even better remedies than are available today and possibly cure of the disease.

Glossary of terms

CTLA-4 = cytotoxic T-lymphocyte antigen 4.

References

1. Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT: **Mortality studies in systemic lupus erythematosus. Results from a single centre. III. Improved survival over 24 years.** *J Rheumatol* 1997, **24**:1061-1065. [general reference]
2. Balow JE, Austin HA, Muenz LR, Joyce KM, Antonovych TT, Klippel JH, Steinberg AD, Plotz PH, Decker JL: **Effect of treatment on the evolution of renal abnormalities in lupus nephritis.** *N Engl J Med* 1984, **311**:491-495. [archival research]
3. Estes D, Christian CL: **The natural history of systemic lupus erythematosus by prospective analysis.** *Medicine* 1971, **50**:85-95. [general reference]
4. Urowitz MB, Gladman DD: **How to improve morbidity and mortality in systemic lupus erythematosus.** *Rheumatology (Oxford)* 2000, **39**:237-243. [general reference]
5. Aringer M, Smolen JS, Graninger WB: **Severe infections in plasmapheresis-treated systemic lupus erythematosus.** *Arthritis Rheum* 1998, **41**:414-420. [general reference]
6. Wakeland EK, Wandstrat AE, Liu K, Morel L: **Genetic dissection of systemic lupus erythematosus.** *Curr Opin Immunol* 1999, **11**:701-707. [key review]
7. Smolen JS: **Experimental therapies in systemic lupus erythematosus.** In *Dubois' Lupus Erythematosus,* 6th edn. Edited by Wallace DJ, Hahn BH. Philadelphia, USA: Lippincott Williams & Wilkins; 2002:1276-1283.
8. Gibofsky A, Kerwar S, Zabriskie JB: **Rheumatic fever. The relationships between host, microbe and genetics.** *Rheum Dis Clin North Am* 1998, **24**:237-259. [key review]
9. Kukreja A, Maclaren NK: **Current cases in which epitope mimicry is considered as a component cause of autoimmune disease: immune-mediated (type 1) diabetes.** *Cell Mol Life Sci* 2000, **57**:534-541. [key review]
10. Guillevin L: **Virus-associated vasculitides.** *Rheumatology (Oxford)* 1999, **38**:588-590. [key review]
11. Guldner HH, Netter HJ, Szostecki C, Jaeger E, Will H: **Human anti-p68 autoantibodies recognize a common epitope of U1 RNA containing small nuclear ribonucleoprotein and influenza B virus.** *J Exp Med* 1990, **171**:819-829. [general reference]
12. Query CC, Keene JD: **A human autoimmune protein associated with U1 RNA contains a region of homology that is cross-reactive with retroviral p30gag antigen.** *Cell* 1987, **51**: 211-220. [general reference]
13. Scofield RH, Dickey WD, Jackson KW, James JA, Harley JB: **A common autoepitope near the carboxyl terminus of the 60-kD Ro ribonucleoprotein: sequence similarity with a viral protein.** *J Clin Immunol* 1991, **11**:378-388. [general reference]
14. Smolen JS, Steiner G: **Are autoantibodies active players or epiphenomena?** *Curr Opin Rheumatol* 1998, **10**:201-206. [key review]
15. James JA, Gross T, Scofield RH, Harley JB: **Immunoglobulin epitope spreading and autoimmune disease after peptide immunization: Sm B/B'-derived PPPGMRPP and PPPGIRGP induce spliceosome autoimmunity.** *J Exp Med* 1995, **181**:453-461. [general reference]
16. James JA, Neas BR, Moser KL, Hall T, Bruner GR, Sestak AL, Harley JB: **Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure.** *Arthritis Rheum* 2001, **44**:1122-1126. [general reference]
17. Murray PG, Young LS: **The role of Epstein-Barr virus in human disease.** *Front Biosci* 2002, **7**:D519-540. [key review]
18. Hopkinson ND, Doherty M, Powell RJ: **Clinical features and race-specific incidence/prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients.** *Ann Rheum Dis* 1994, **153**:675-680. [general reference]
19. Jones DS, Barstad PA, Feild MJ, Hachmann JP, Hayag MS, Hill KW, Iverson GM, Livingston DA, Palanki MS, Tibbetts AR, *et al.*: **Immunospecific reduction of antioligonucleotide antibody-forming cells with a tetrakis-oligonucleotide conjugate (LJP 394), a therapeutic candidate for the treatment of lupus nephritis.** *J Med Chem* 1995, **38**:2138-2144. [general reference]
20. Weisman MH, Blustein HG, Berner CM: **Reduction in circulating dsDNA antibody titer after administration of LJP 394.** *J Rheumatol* 1997, **24**:314-318. [general reference]
21. Lu L, Kaliyaperumal A, Boumpas DT, Datta SK: **Major peptide autoepitopes for nucleosome-specific T cells of human lupus.** *J Clin Invest* 1999, **104**:345-355. [general reference]
22. Voll RE, Roth EA, Girkotaite I, Fehr H, Herrmann M, Lorenz HM, Kalden JR: **Histone-specific Th0 and Th1 clones derived from systemic lupus erythematosus patients induce double-stranded DNA antibody production.** *Arthritis Rheum* 1997, **40**: 2162-2171. [general reference]
23. Schett G, Rubin RL, Steiner G, Hiesberger H, Muller S, Smolen J: **The lupus erythematosus cell phenomenon: comparative analysis of antichromatin antibody specificity in lupus erythematosus cell-positive and -negative sera.** *Arthritis Rheum* 2000, **43**:420-428. [general reference]
24. Datta SK, Kaliyaperumal A, Desai-Mehta A: **T cells of lupus and molecular targets for immunotherapy.** *J Clin Immunol* 1997, **17**:11-20. [general reference]
25. Sakane T, Steinberg AD, Green I: **Studies of immune functions of patients with systemic lupus erythematosus. I. Dysfunction of suppressor T-cell activity related to impaired generation of, rather than response to, suppressor cells.** *Arthritis Rheum* 1978, **21**:657-664. [general reference]
26. Shevach EM, McHugh RS, Thornton AM, Piccirillo C, Natarajan K, Margulies DH**: Control of autoimmunity by regulatory T cells.** *Adv Exp Med Biol* 2001, **490**:21-32. [general reference]
27. Bluestone JA: **Is CTLA-4 a master switch for peripheral T cell tolerance?** *J Immunol* 1997, **158**:1989-1993. [key review]
28. Finck BK, Linsley PS, Wofsy D: **Treatment of murine lupus with CTLA4Ig**. *Science* 1994, **265**:1225-1227. [general reference]
29. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, Menter A, Lowe NJ, Krueger G, Brown MJ, Weiner RS, Birkhofer MJ, Warner GL, Berry KK, Linsley PS, Kreuger JG, Ochs HD, Kelley SL, Kang S: **CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris.** *J Clin Invest* 1999, **103**:1243-1252. [general reference]

30. Daikh DI, Wofsy D: **Effects of anti-B7 monoclonal antibodies on humoral immune responses.** *J Autoimmun* 1999, **12**:101-108. [general reference]
31. Waisman A, Ruiz PJ, Israeli E, Eilat D, Konen-Waisman S, Zinger H, Dayan M, Mozes E: **Modulation of murine systemic lupus erythematosus with peptides based on complementarity determining regions of a pathogenic anti-DNA monoclonal antibody.** *Proc Natl Acad Sci USA* 1997, **94**:4620-4625. [general reference]
32. Rose NR, Bona C: **Defining criteria for autoimmune diseases (Witebsky's postulates revisited).** *Immunol Today* 1993, **14**: 426-430. [key review]
33. Monia H, Holers VM, Li B, Fung Y, Mariathasan S, Goellner J, Strauss-Schoenberger J, Karr RW, Chaplin DD: **Markedly impaired humoral immune response in mice deficient in complement receptors 1 and 2.** *Proc Natl Acad Sci USA* 1996, **93**: 3357-3361. [general reference]
34. Wang Y, Hu O, Madre JA: **Amelioration of lupus-like autoimmune disease in NZB/W F1 mice after treatment with a blocking monoclonal antibody specific for complement component C5.** *Proc Natl Acad Sci USA* 1996, **93**:8563-8568. [general reference]
35. Weisman HF, Bartow MK, Leppo MP, Boyle MP, Marsh HC Jr, Carson GR, Roux KH, Weisfeldt ML, Fearon DT: **Recombinant soluble CR1 suppressed complement activation, inflammation and necrosis associated with reperfusion of ischemic myocardium.** *Trans Assoc Am Physicians* 1990, **103**:64-72. [general reference]
36. Clynes R, Dumitru C, Ravetch JV: **Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis.** *Science* 1998, **279**:1052-1054. [general reference]
37. Watanabe H, Sherris D, Gilkeson GS: **Soluble CD16 in the treatment of murine lupus nephritis.** *Clin Immunol Immunopathol* 1998, **88**:91-95. [general reference]
38. Bolland S, Ravetch JV: **Inhibitory pathways triggered by ITIM-containing receptors.** *Adv Immunol* 1999, **72**:149-177. [general reference]
39. Samuelsson A, Towers TL, Ravetch JV: **Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor.** *Science* 2001, **291**:445-446. [general reference]
40. Levy Y, Sherer Y, George J, Rovensky J, Lukac J, Rauova L, Poprac P, Langevitz P, Fabbrizzi F, Shoenfeld Y: **Intravenous immunoglobulin treatment of lupus nephritis.** *Semin Arthritis Rheum* 2000, **29**:321-327. [key review]
41. Lehrnbecher T, Foster CB, Zhu S, Leitman SF, Goldin LR, Huppy K, Chanock SJ: **Variant genotypes of low affinity Fcgamma receptors in two control populations and a review of low-affinity Fcgamma receptor polymorphisms in control and disease populations.** *Blood* 1999, **94**:4220-4232. [general reference]
42. Davis JC, Manzi S, Yarboro C, Rairie J, McInnes I, Averthelyi D, Sinicropi D, Hale VG, Balow J, Austin H, Boumpas DT, Klippel JH: **Recombinant human DNaseI (rhDNase) in patients with lupus nephritis**. *Lupus* 1999, **8**:68-76. [general reference]
43. van Bruggen MCJ, Walgreen B, Rijke RPM, Corsius MJAMM, Assmann KJM, Smeenk RJT, van Dedem GWK, Kramers K, Berden JHM: **Heparin and heparinoids prevent the binding of immune complexes containing nucleosomal antigens to the GBM and delay nephritis in MRL/lpr mice.** *Kidney Int* 1996, **50**: 1555-1564. [general reference]
44. Gaynor B, Putterman C, Valadon P: **Peptide inhibition of glomerular deposition of an anti-DNA antibody.** *Proc Natl Acad Sci USA* 1997, **94**:1955-1960. [general reference]
45. Hooks JJ, Moutsopoulos HM, Geis SA, Stahl NI, Decker JL, Notkins AL: **Immune interferon in the circulation of patients with autoimmune disease.** *N Engl J Med* 1979, **301**:5-8. [general reference]
46. Machold KP, Smolen JS: **Interferon-gamma induced exacerbation of systemic lupus erythematosus.** *J Rheumatol* 1990, **17**: 831-832. [general reference]
47. Graninger WB, Hassfeld W, Pesau BB, Machold KP, Zielinski CC, Smolen JS: **Induction of systemic lupus erythematosus by interferon-gamma in a patient with rheumatoid arthritis.** *J Rheumatol* 1991, **18**:1621-1622. [general reference]
48. Seery JP, Carroll JM, Cattell V, Watt FM: **Antinuclear autoantibodies and lupus nephritis in transgenic mice expressing interferon gamma in the epidermis.** *J Exp Med* 1997, **186**: 1451-1459. [general reference]
49. Balomenos D, Rumold R, Theofilopoulos AN: **Interferon-gamma is required for lupus-like disease and lymphoaccumulation in MRL-lpr mice.** *J Clin Invest* 1998, **101**:364-371. [general reference]
50. Ozmen L, Roman D, Fountoulakis M, Schmid G, Ryffel B, Garotta G: **Experimental therapy of systemic lupus erythematosus: the treatment of NZB/W mice with mouse soluble interferon-gamma receptor inhibits the onset of glomerulonephritis.** *Eur J Immunol* 1995, **25**:6-12. [general reference]
51. Lawson BR, Prud'homme GJ, Chang Y, Gardner HA, Kuan J, Kono DH, Theofilopoulos AN: **Treatment of murine lupus with cDNA encoding IFN-gammaR/Fc.** *J Clin Invest* 2000, **106**:207-215. [general reference]
52. Santiago ML, Fossati L, Jacquet C, Muller W, Izui S, Reininger L: **Interleukin-4 protects against a genetically linked lupus-like autoimmune syndrome.** *J Exp Med* 1997, **185**:65-70. [general reference]
53. Romagnani S: **The Th1/Th2 paradigm.** *Immunology Today* 1997, **18**:263-266. [key review]
54. Studnicka-Benke A, Steiner G, Petera P, Smolen JS: **Tumour necrosis factor alpha and its soluble receptors parallel clinical disease and autoimmune activity in systemic lupus erythematosus.** *Br J Rheumatol* 1996, **35**:1067-1074. [general reference]
55. Chouchakova N, Skokowa J, Baumann U, Tschernig T, Philippens KM, Nieswandt B, Schmidt RE, Gessner JS: **Fc gamma RIII-mediated production of TNF-alpha induces immune complex alveolitis independently of CXC chemokine generation.** *J Immunol* 2001, **166**:5193-5200. [general reference]
56. Cobb RR, Molony JL: **Interleukin-1beta expression is induced by adherence and is enhanced by Fc-receptor binding to immune complex in THP-1 cells.** *FEBS Lett* 1996, **394**:241-246. [general reference]
57. Yokoyama H, Kreft B, Kelley VR: **Biphasic increase in circulating and renal TNF-alpha in MRL-lpr mice with differing regulatory mechanisms.** *Kidney Int* 1995, **47**:122-130. [general reference]
58. Le Hir M, Haas C, Marino M, Ryffel B: **Prevention of crescentic glomerulonephritis induced by anti-glomerular membrane antibody in tumor necrosis factor-deficient mice.** *Lab Invest* 1998, **78**:1625-1631. [general reference]
59. Jacob CO, McDevitt HO: **Tumour necrosis factor-alpha in murine autoimmune ´lupus´ nephritis.** *Nature* 1988, **331**:356-358. [general reference]
60. Hanauer SB: **Review article: safety of infliximab in clinical trials.** *Aliment Pharmacol Ther* 1999, **13 (Suppl 4)**:16-22. [key review]
61. Gunnarsson I, Kanerud L, Pettersson E, Lundberg I, Lindblad S, Ringertz B: **Predisposing factors in sulphasalazine-induced systemic lupus erythematosus.** *Br J Rheumatol* 1997, **36**: 1089-1094. [general reference]
62. Gough A, Chapman S, Wagstaff K, Emery P, Elias E: **Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome.** *BMJ* 1996, **312**:169-172. [key review]
63. Charles PJ, Smeenk RJT, DeJong J, Feldmann M, Maini RN: **Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trrials.** *Arthritis Rheum* 2000, **43**:2383-2390. [general reference]
64. Smolen JS, Steiner G, Breedveld FC, Kalden JR, Lipsky PE, Maini RN, St Clair EW, Harriman G, Schaible T: **Anti-TNF alpha therapy and drug-induced lupus-like syndrome.** *Ann Rheum Dis* 1999, **58 (Suppl)**:S217. [general reference]
65. 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**:1105-1111. [general reference]
66. Pisetsky DS: **Tumor necrosis factor alpha blockers and the induction of anti-DNA autoantibodies.** *Arthritis Rheum* 2000, **43**:2381-2382. [Editorial]
67. Aringer M, Steiner G, Graninger W, Smolen JS: **Role of tumor necrosis factor alpha and potential benefit of tumor necrosis factor blockade treatment in systemic lupus erythematosus: comment on the editorial by Pisetsky.** *Arthritis Rheum* 2001, **44**:1721-1722. [general reference]

68. Schneeweiss B, Graninger WB: **Treatment of mixed connective tissue disease with infliximab [abstract].** *Clin Exp Rheumatol* in press.
69. Manna SK, Mukhopadhyay A, Aggarwal BB: **Leflunomide suppresses TNF-induced cellular responses: effects on NF-kappa B, activator protein-1, c-Jun N-terminal protein kinase, and apoptosis.** *J Immunol* 2000, **165**:5962-5969. [general reference]
70. Petera P, Manger B, Manger K, Rosenburg R, Smolen JS, Kalden JR: **A pilot study of leflunomide in systemic lupus erythematosus (SLE).** *Arthritis Rheum* 2000, **43(Suppl)**:S241. [general reference]
71. Remer CF, Weisman MH, Wallace DJ: **Benefits of leflunomide in systemic lupus erythematosus: a pilot observational study.** *Lupus* 2001, **10**:480-483. [general reference]
72. Lee JC, Kassis S, Kumar S, Badger A, Adams JL: **p38 mitogen-activated protein kinase inhibitors-mechanisms and therapeutic potentials.** *Pharmacol Ther* 1999, **82**:389-397. [general reference]
73. Firestein GS, Manning AM: **Signal transduction and transcription factors in rheumatic disease.** *Arthritis Rheum* 1999, **42**: 609-621. [general reference]
74. Marmont AM: **Stem cell transplantation for severe autoimmune diseases. Progress and problems.** *Haematologia* 1998, **83**:733-743. [general reference]
75. Machold in press. [general reference]
76. Smolen JS, Strand V, Cardiel M, Edworthy S, Furst D, Gladman D, Gordon C, Isenberg DA, Klippel JH, Petri M, Simon L, Tugwell P, Wolfe F: **Randomized clinical trials and longitudinal observational studies in systemic lupus erythematosus: consensus on a preliminary core set of outcome domains.** *J Rheumatol* 1999, **26**:504-507. [general reference]