

IMMUNOPHARMACOLOGY: A GUIDE TO NOVEL THERAPEUTIC TOOLS

Francesco Roselli

Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy

Emilio Jirillo

Department of Internal Medicine, Immunology and Infectious Disease, University of Bari, Italy

National Institute for Digestive Disease, Castellana Grotte, Bari, Italy

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Summary

Immunopharmacology is that area of pharmacological sciences dealing with the selective modulation (i.e. upregulation or downregulation) of specific immune responses and, in particular, of immune cell subsets. For many years, biological response modifiers or immunomodulating agents have been used in clinical practice despite severe side effects. In recent years, a precise knowledge of their activity and great advances in biotechnology have made available new classes of these drugs with much improved selectivity, now entering clinical use. In the present review, emphasis will be placed on the major immunomodulators according to their application in various pathologies.

Anti CD-20 monoclonal antibody (MAb) (Rituximab) is used in oncology to induce B cell depletion, but its efficacy has been proven also for therapy of Rheumatoid Arthritis (RA), Autoimmune Haemolytic Anaemia, Graft Versus Host Disease (GVHD), refractory Myasthenia Gravis.

Anti α 4 integrin antibody (Natalizumab) and anti CD11a (Efalizumab) are effective in blocking T cell adhesion to endothelial cells and extravasation: Natalizumab proved effective as a Multiple Sclerosis (MS), Crohn Disease (CD) and Psoriasis treatment, but because of unexpected side effects (reactivation of latent JC virus) it is currently withheld. Efalizumab proved effective for Psoriasis treatment.

Costimulation antagonists interfere with CD28 (Abatacept, Betalacet) or with CD2 (Alefacet) signalling, preventing full T cell activation and favouring T cell anergy and tolerance. Abatacept proved to be effective for RA therapy, and Betalacet has also been tested for prevention of acute allograft rejection. On the other hand, Alefacet seems to be effective for Psoriasis therapy.

MAb directed against Interleukin-2 receptors (Basiliximab, Daclizumab) have been successfully used as adjunctive therapy for the prevention of allograft rejection, and are under study for several autoimmune conditions.

TNF antagonists (Infliximab, Adalimumab, Etanercept) have gained widespread acceptance for therapy of RA, ankylosing spondylitis and CD, showing variable efficacy in other granulomatous autoimmune conditions. However, these agents increase the risk of tuberculosis reactivation. Likewise, Interleukin (IL)-1 antagonist (Anakinra) proved moderately effective on RA therapy and showed promising effects in rarer inflammatory conditions.

IL-6 antagonist (Tocilizumab) proved effective for RA and CD therapy, and is currently under testing for other conditions such as Castleman's Disease.

In the field of allergic disease, anti IgE monoclonal antibody (Omalizumab) gained approval for the prevention of asthma reacutization in high risk patients, and is under testing for other life-threatening allergic disease.

Immunopharmacological approaches in oncology have been not as successful as for autoimmune disease. IL-2 infusion is able to induce complete responses in a small subset of patients affected by renal cell cancer or melanoma, however, recent trials

using lesion-restricted injection seem to produce far better results. A chimeric derivative of IL-2 conjugated to difteria toxin (Denileukin Diftitox) recently proved effective for some T cell malignancy therapy, but also showed some efficacy for GVHD treatment. Trials of other cytokines so far have been disappointing.

Many other cytokines and MAb have been used in small preliminary trials with promising results, and many more agents are expected to enter clinical efficacy in the next years.

1. Introduction

Immunopharmacology is one of the youngest areas of pharmacology. The first generation of immune-modulating agents included molecules drawn from oncology. These drugs, such as methotrexate, azathyoprine and cyclophosphamide, dampened immune responses through their anti-proliferative action. The second generation, notably cyclosporine, exploited some natural agents able to block several signal transduction pathways. Many of these agents were plagued by several severe side effects, mainly due to their ability to affect every fast-proliferating cell type (alkylating agents, purine and pyrimidine analogues) or to affect signal transduction in several organs and tissues, with toxic effects (e.g. cyclosporine). Moreover, many of these agents were quite non-specific in their ability to depress immune function, thus generating a profound impairment in biological responses.

However, in recent years, advances in our knowledge about how the immune system works have identified several molecular targets suitable for more selective modulation of immune function. These targets can be broadly divided into surface molecules and soluble mediators. Surface molecules play a fundamental role in antigen recognition, immune response activation, homing and effector functions. Soluble mediators are involved in lymphocyte proliferation and differentiation, inflammatory response and cell recruitment. Likewise, there are currently two broad categories of agents suitable for targeting these molecules: small-molecule drugs and monoclonal antibodies (MAb). While small molecule drugs offer the advantage of potential oral administration and use in an outpatient setting, their experimental designing and testing are quite complex. MAb are clearly bulky and need to be injected or infused, but their half-life is usually longer. Moreover, MAb are usually highly selective and can be produced faster using biotechnological approaches. The first generation of antibodies entering clinical trials were murine MAb or antisera obtained in rabbits or horses. These antibodies often caused adverse events and allergic reactions and were highly immunogenic for human patients. In fact, their infusion often elicited an immune response against the antibody itself, preventing their use for longer periods. In particular, this anti-antibody immune response caused either the failure of the antiserum or, worse, the onset of severe allergic reactions or serum sickness. Further refinements have allowed for either humanized (i.e. with murine antibody parts replaced by human parts) or fully human MAb, which are far less immunogenic than their original murine counterparts and thus suitable for clinical purposes. The main disadvantage of this approach stems from our limited understanding of the immune system itself. In fact, highly specific agents designed after extensive testing in murine models have actually failed to be up to the task in human patients, proving sometimes to actually worsen the condition they were supposed to

treat. On the other hand, some agents designed for a specific pathological condition were even more effective in a completely different setting. Taken together, MAbs are the most successful group of biological drugs available, and many of them won approval for clinical use in the last few years. It is not completely surprising that most, if not all, of these MAbs work as immune suppressors. In fact, they usually engage their target molecule but they do not act as physiological ligands, just as antagonists, preventing the binding of the physiological counterpart. Furthermore, retaining their antibody properties, these molecules can activate cell-mediated cytotoxicity or quick removal of complexes from the circulation. However, at least one drug targeted against inhibitory T cell subset may actually result in immune response stimulation.

Far more difficult to produce are immune stimulating drugs. Cloning and expression technology has made a large array of cytokines available in highly purified form, many of which have made their way to clinical trials. The intricacies of the cytokine network have hindered a more widespread application of this approach. In fact, many cytokines have overlapping and sometimes redundant roles; this implies that infusion of a single cytokine may be not able to elicit the type of response for which that cytokine is putatively responsible in *in vitro* models. Furthermore, cytokine infusion can result in massive and non-specific activation of the immune system, resulting in a clinical effect resembling overwhelming infection or septic shock. Nevertheless, at least for one cytokine (namely, Interleukin-2), some benefits in clinical trials have been observed, and further refinement of administration route and schedule are yielding promising results.

A third class of specific biotechnological agents includes chimeras, in which one cytokine or one antibody is conjugated to bacterial toxins or to radioactive substances. This approach delivers an increased toxic effect (radiation or toxins) with the high selectivity produced by the antibody/antigen or cytokine/receptor interaction. In principle, it would be possible to selectively affect only one limited subset of immune cells. However, several technical hurdles have delayed the development of these agents, and so far only one of them (namely, the interleukin-2/difteria toxin chimerical protein) has gained approval for clinical use.

To deal with the burgeoning field of immunopharmacology, some limitations are required. We have restricted the scope of this review to the latest highly specific drugs already used in clinical trials or which have obtained formal approval only in recent years. Thus, some well known drugs for which considerable clinical experience is already available (for example interferon α and β) will not be discussed; molecules for which only data from *in vitro* or murine models are available will also not be considered. For other molecules (including small-molecule drugs like rapamycin, thalidomide and leflunomide) readers are referred to a number of exhaustive reviews. Likewise, vaccination (against infectious agents or neoplastic antigens), dendritic-cell based therapy, adoptive T cell transfer and genetically engineered immune cells approaches will not be discussed.

2. B cell targeted immunotherapy: Rituximab

Rituximab (RTX) is an engineered chimeric antibody comprising human IgG1- κ costant

region and complementarity determining regions from a mouse high affinity MAb directed against CD20 protein found on B cell lymphocytes. CD 20 function is not completely understood, but several lines of evidence have suggested its involvement in B cell activation and Ca^{++} flux control. CD is widely expressed on pre-B and B cells, and its expression is lost during the differentiation to plasma cells. CD20 is not internalized after RTX binding, and it is neither shed from cell surface nor produced in soluble form. These two features make CD 20 an attractive molecule to target B cells.

Since CD20 is widely expressed only on pre-B and B cells, RTX selectively targets B cells without affecting T lymphocytes and other bone-marrow derived cell types. RTX infusion results in depletion of B cells, both in human and in murine models, via at least three mechanisms, namely antibody-dependent cell-mediated cytotoxicity, antibody-dependent complement-mediated toxicity and inhibition of CD20 function causing B cell apoptosis. Most *in vivo* data point to the first as the most relevant mechanism involved. Experience gathered in oncology suggests that depletion of B cells is sustained up to six months and repopulation occurs after 9 to 12 months. The limited capacity to affect terminally differentiated plasma cells may explain the sustained levels of serum immunoglobulin during RTX therapy despite the almost complete depletion of B cells.

RTX is infused at a recommended dose of 375 mg/m^2 once weekly for four weeks for lymphoma therapy. Variable doses have been tested in clinical trials for autoimmune disease, usually about 2g infused in two to four weeks (up to 500mg for each infusion). RTX is approved for therapy of B cell malignancies, originally for indolent and follicular lymphomas, alone or, with better outcomes, in combination with different regimens of chemotherapy. RTX is also effective in addition to a standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen in aggressive non-Hodgkin lymphomas.

More recently, RTX has been investigated for therapeutic value in autoimmune disease. RTX was first tested in Rheumatoid Arthritis (RA) therapy. The role of B cells in RA pathogenesis has recently been uncovered, and at least three mechanisms have been proposed: B cells may act as antigen presenting cells (APC) and participate in cognate stimulation of T cells; B cells are directly involved in pannus formation and can secrete proinflammatory cytokine *in situ*; B cells contribute to RA pathogenesis by producing autoreactive antibodies, such as rheumatoid factor (RF), the most known and the most correlated with disease activity. In the first open label trial of RA, RTX was infused to five patients who proved to be refractory to any other treatment; they were also given cyclophosphamide and prednisone. Response to therapy was assessed according to American College of Rheumatologist (ACR) criteria, i.e a 20% (ACR20), 50% (ACR50), or 75% (ACR75) reduction in a composite score involving, among other features, the number and the severity of swollen joints. All five patients showed a marked improvement (all of them reached ACR50 criterion and 3 out of 5 reached the ACR70 threshold) that was sustained up to one year after treatment in at least two patients, even in the presence of recovery of circulating B cell levels. A larger, double-blinded trial enrolled 161 patients with refractory RA to compare RTX with methotrexate (MTX), RTX+MTX, RTX+ cyclophosphamide regimens. The evaluation of patients after 24 weeks from RTX infusion showed that both combination therapy

RTX-cyclophosphamide and RTX+MTX were highly effective, with 84 and 80% of patients satisfying the ACR20 criterion and 45 and 50% satisfying the ACR50 criterion respectively, compared to 33 and 10 in the MTX-only group. These results have been supported by results in small open label studies in which highly refractory patients with RA have been enrolled. However, the large variability of RTX doses used for RA therapy calls for larger double blind trials before RTX may be used widely in clinical practice. RTX appears to be safe, and the commonest adverse effects are usually mild, and include infusion related hypotension, fever and rash. Two cases of pneumonia (one of which proved to be fatal) occurred in RTX-treated groups, suggesting that, like all immunosuppressants, RTX may increase susceptibility to infections. RTX therapy proved effective also in repeated cycles: 37 patients have been treated during 5 years with repeated cycles of RTX, with an average time-to retreatment of 20 months. However, 13 patients were withdrawn due to the brevity of the complete absence of response.

Other autoimmune conditions characterized by a prominent role for auto-antibodies in pathogenesis have been reported to benefit from RTX-induced B cell depletion. They include IgM-mediated neuropathies, idiopathic thrombocytopenic purpura (ITP), autoimmune haemolytic anaemia (AIHA), systemic lupus erythematosus (SLE), dermatomyositis and type-II mixed cryoglobulinemia. However, in many of these conditions, only small trials or case series are available. Two trials were conducted in AIHA patients after initial encouraging case reports; RTX-treated patients had a response rate between 83 and 100%, with a duration of response up to 2.5 years. In ITP early trials, 25% of patients resistant to all treatments (including splenectomy) experienced objective responses; interestingly, this happened in absence of changes in serum immunoglobulin levels. In a recent retrospective analysis of 25 patients, overall response rate for refractory ITP and AIHA treated with RTX approached 100%, and the mean progression-free survival was 3.7 years in treated patients, compared to 0.1 years in patients receiving standard therapy. All in all, the pooling analysis of reports on 319 patients with refractory ITP treated with RTX revealed a platelet levels response in 62.5% of patients , with a 2.9% of mortality during treatment.

Some case reports have provided support for the use of RTX in refractory Myasthenia Gravis. In one paediatric case, RTX therapy resulted in marked improvement of symptoms after 4 weeks and caused the decrease of anti-acetylcholine receptor antibody titres. RTX was tested for SLE therapy in two small trials. In the first phase I/II trial, enrolling 18 patients with active disease, a dose-escalation design was adopted. Ten patients were reported to achieve satisfactory B cell depletion and in these patients a significant clinical response, more prominent in skin and joint manifestation, was observed. However, in patients showing only poor B cell depletion, no clinical benefit was detected. In a second small trial, six patients were treated with RTX and CTX plus prednisone; five of them experienced a good clinical response, but two relapsed after 6 months, at the time of B cell repopulation. In the first trial, no serologic response was observed; in the second trial, convincing serologic response was observed in only two patients. Dramatic and very sustained responses have also been reported in five patients with refractory dermatomyositis treated with RTX monotherapy, without any significant adverse effect.

Likewise, RTX combined with intravenous Ig proved highly effective in patients with refractory pemphigus vulgaris involving 30% or more of their body-surface area; in a small trial involving 11 patients, 9 experienced prolonged remission lasting up to 37 months after treatment without any additional immunosuppressive therapy.

RTX therapy has also been tested in small trials for graft-versus-host disease (GVHD), in which B cells may act as antigen-presenting cells (APC), thus contributing to T cell activation. In this setting, RTX efficacy is lower than expected. However, in non-Hodgkin lymphoma patients undergoing allogenic stem cell transplantation, the rate of severe GVHD was greatly reduced after treatment with RTX (18% compared to 51% in untreated patients). This result underscores the complexity of pathogenic processes involved in GVHD, and suggests that further studies are required before establishing RTX therapy for GVHD, and in acute rejection of renal grafts. In both cases results were promising, but further studies are required before establishing a role for RTX in clinical practice.

3. Lymphocyte trafficking inhibitors: Natalizumab and Efalizumab

Leukocyte trafficking plays a fundamental role in immune cell function, being involved in lymphocyte homing and maturation and in recruitment of immune cells in the site of inflammation. Lymphocyte trafficking involves several steps including rolling, adhesion to endothelial cells and extravasation. These processes are fundamental for immune responses, and genetic defects in the molecules involved result in profound immunodeficiency. Thus, adhesion and extravasation are, in principle, suitable targets for immunomodulatory agents. In recent years, two partner adhesion molecules have been identified as key players in these processes: the Leukocyte Function-associated Antigen-1 (LFA-1)/Inter Cellular Adhesion Molecule-1 (ICAM-1) and Very Late Antigen-4 (VLA-4) belonging to the $\alpha 4$ integrin family/Vascular Cell Adhesion Molecule (VCAM). Both of them have been targeted by specific inhibitors, which are therefore able to inhibit lymphocyte movement across endothelia. At least two MAb reached clinical ground recently and they are discussed in detail below.

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Bibliography

Amati L, Caradonna L, Leandro G, Magrone T, Minenna M, Faleo G, Pellegrino NM, Jirillo E, Caccavo D (2005). Immune abnormalities and endotoxemia in patients with ulcerative colitis and in their first degree relatives: attempts at neutralising endotoxin-mediated effects. *Curr Pharm Design* 9:1918-1923 [A complementary view of CD pathogenesis]

Amati L, Passeri ME, Mastronardi ML, Jirillo E (2004) Anti Tumor Necrosis Factor α monoclonal

antibody (Infliximab) therapy in patients with inflammatory bowel disease: applications and side effects. *Drug Design Rev Online* 1:111-117 [A review of immunological effects of Infliximab]

van Assche G, Vermeire S, Rutgeerts P (2005) Medical treatment of inflammatory bowel diseases *Curr Opin Gastroenterol* 21:443–447 [A review discussing TNF antagonist for medical management of Crohn disease]

Boye J, Elter T, Engert A (2004) An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab *Ann Oncology* 14: 520–535 [A comprehensive discussion of current and future Rituximab applications in clinical practice]

Caradonna L, Amati L, Magrone T, Pellegrino NM, Jirillo E, Caccavo D (2000). Enteric bacteria, lipopolysaccharides and related cytokines in inflammatory bowel disease: biological and clinical significance. *J Endotoxin Res* 6:205-214 [New insights into the role of bacteria and their components on IBD pathogenesis and possible therapeutic approaches]

Cartron G, Watier H, Golay J, Solal-Celigny P (2004) From the bench to the bedside: ways to improve rituximab efficacy. *Blood* 104:2635-2642 [A very detailed discussion of CD20 and anti-CD20 monoclonal antibody (Rituximab) role in health and disease]

Church AC (2003) Clinical advances in therapies targeting the interleukin-2 receptor *Q J Med* 96:91–102 [An interesting summary of Daclizumab and Basiliximab use in clinical practice]

Dranoff G (2004) Cytokines in cancer pathogenesis and cancer therapy. *Nature Immunol* 4;11-22

[A comprehensive review of several approaches exploiting cytokine for cancer therapy]

Dinarello CA (2005) Blocking IL-1 in systemic inflammation. *J Exp Med* 201: 1355–1359

[A mechanistic discussion of IL-1 role in several genetic and non-genetic inflammatory conditions]

Eklund JW, Kuzel TM (2004) A review of recent findings involving interleukin-2-based cancer therapy. *Curr Opin Oncol* 16:542–546. [Some promising results from the la test trials]

Furst DE (2005) Anakinra: review of recombinant human interleukin- I receptor antagonist in the treatment of rheumatoid arthritis. *Clin Therap* 26: 1960-1975 [A comprehensive discussion about Anakinra role in RA therapy]

Hansson GK (2005). Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med.* 352:1685-95 [The role of inflammation in atherosclerosis and a discussion of possible roles of immunomodulatory drugs]

Hershberger RE, Starling RC , Eisen HJ, Bergh CH, Kormos RL, Love RB, Van Bakel A, Gordon RD, Popat R, Cockey L, Mamelok RD (2005) Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 352:2705-13. [One recent, well-organized trial for Daclizumab therapy after cardiac transplantation]

Ho VT, Zahrieh D, Hochberg E, Micale E, Levin J, Reynolds C, Steckel S, Cutler C, Fisher DC, Lee SJ, Alyea EP, Ritz J, Soiffer RJ, Antin JH (2004) Safety and efficacy of denileukin diftitox in patients with steroid-refractory acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Blood* 4:1224-1226 [Some promising results of Denileukin diftitox in graft-versus-host disease]

Hodak E, David M (2004) Alefacept: a review of the literature and practical guidelines for management. *Dermatol therapy* 17:383-392. [Comprehensive review of clinical data about CD2 antagonist Alefacept]

Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C (2005) The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation *J Allergy Clin Immunol* 15:459-65 [A review of anti-IgE therapy in allergic and non-allergic disease]

Kleinschmidt-DeMasters BK, Tyler KL (2005) Progressive Multifocal Leukoencephalopathy complicating treatment with natalizumab and Interferon Beta-1a for multiple sclerosis. *N Engl J Med* 353:369-74. [One of the reports identifying Natalizumab deadly side effects]

Leonardi CG (2004) Efalizumab in the treatment of psoriasis. *Dermatol Therapy* 17:393-400

[A comprehensive review of Efalizumab efficacy in psoriasis]

Ishimoto N, Kishimoto T. Interleukin 6: from bench to bedside (2006). *Nat Clin Pract Rheumatol*. 2006

2(11):619-26. [A primer for anti-IL-6 therapy in inflammatory conditions]

Pollard L, Choy E (2005) Rheumatoid arthritis: non-tumor necrosis factor targets. *Curr Opin Rheumatol* 17:242—246. [Concise review of several non-TNF based immunopharmacological approaches in RA therapy]

Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators. (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 354:899-910. [The largest clinical trial to date on Natalizumab therapy in Multiple Sclerosis]

Poole JA, Matangkasombut P, Rosenwasser LJ (2005) Targeting the IgE molecule in allergic and asthmatic diseases: review of the IgE molecule and clinical efficacy. *J Allergy Clin Immunol* 115: S376-S383 [A detailed review of Omalizumab efficacy and clinical use]

Portielje JEA, Lamers CHL, Kruit WHJ, Sparreboom A, Bolhuis RH, Stoter G, Huber C, Gratama JW (2003) Repeated administrations of Interleukin (IL)-12 are associated with persistently elevated plasma levels of IL-10 and declining IFN- γ , tumor necrosis factor- α , IL-6, and IL-8 responses. *Clin Cancer Res* 9:76-83 [An interesting discussion of the complex immunological responses to IL-12 injection]

Roselli F, Livrea P, Jirillo E (2006). Voltage-gated Sodium channel blockers as immunomodulators. *Recent Pat CNS Drug Dis* 1:83-92 [Immunomodulatory properties of anticonvulsants and antiarrhythmic drugs]

Rudermann EM, Pope RM (2005) The evolving clinical profile of abatacept (CTLA4-Ig): a novel co-stimulatory modulator for the treatment of rheumatoid arthritis. *Arthritis Res Ther* 7 (Suppl 2):S21-S25 [A summary of antiCD28 agents as RA therapy]

Simmons DL (2005) Anti-adhesion therapies. *Curr Op Pharmacol* 5:398-404 [Concise review of Natalizumab and Efalizumab mechanism of action]

Shaw T, Quan J, Totoritis MC (2003) B cell therapy for rheumatoid arthritis: the rituximab (anti-CD20) experience. *Ann. Rheum.* 62:55-59 [Concise discussion of Rituximab potential use in RA therapy]

Biographical Sketches

Francesco Roselli received his Medical Degree in 2001 and specialization in Neurology in 2006, both at Bari University (Italy) and is currently PhD student in Neurology in Bari University and visiting scientist at Max Planck Institute for Psychiatry in Munich (Germany).

Emilio Jirillo is a full Professor of Immunology at Bari University and Scientific Director of the National Institute for Digestive Diseases, Castellana Grotte, Bari (Italy).