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REVIEW

Biologics in organ transplantation

Eugenia K. Page, Wasim A. Dar and Stuart J. Knechtle

Department of Surgery, Emory University Hospital, Atlanta, GA, USA

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Correspondence
Stuart J. Knechtle, 101 Woodruff Circle, 5105-WMB, Atlanta, GA 30322, USA.
Tel.: 404 712 9910;
fax: 404 727 3660;
e-mail: stuart.knechtle@emoryhealthcare.org

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Summary

The last two decades have witnessed a pandemic in antibody development, with over 600 entering clinical studies and a total of 28 approved by the FDA and European Union. The incorporation of biologics in transplantation has made a significant impact on allograft survival. Herein, we review the armamentarium of clinical and preclinical biologics used for organ transplantation – with the exception of belatacept – from depleting and IL-2R targeting induction agents to costimulation blockade, B-cell therapeutics, BAFF and complement inhibition, anti-adhesion, and anti-cytokine approaches. While individual agents may be insufficient for tolerance induction, they provide possibilities for reduction of steroid or calcineurin inhibitor use, alternatives to rejection episodes refractory to conventional therapies, and specialized immunosuppression for highly sensitized patients.

History of biologics

This year marks the 50th anniversary of immunosuppression used in transplantation, with the introduction of 6-mercaptopurine and azathioprine in kidney recipients in 1962 [1]. The subsequent incorporation of chemical and biological immunosuppressive agents has revolutionized organ transplantation, allowing many recipients to enjoy years of graft success. The use of biologics – therapeutic agents derived from microbials, proteins, antibodies, cells, and tissues – has shown great promise for the field of transplantation.

The last few decades have witnessed a pandemic in antibody development, with over 600 entering clinical studies and a total of 28 approved by the European Union and US Food and Drugs Administration by 2010 [2,3]. They comprise the majority of induction agents, and those being developed for maintenance immunosuppression (i.e. costimulation blockade). The prospect of avoiding side effects related to long-term calcineurin inhibition or steroid use has driven the development of agents such as cytotoxic T-lymphocyte antigen (CTLA) 4-based CD28/B7 costimulation inhibitor belatacept. The targeting of specific molecules and immunologic pathways has also led the field to adopt biologics from oncology, rheumatology, and dermatology in several preclinical studies. Herein, we review the armamentarium of clinical and preclinical biologics used for organ transplantation (Fig. 1). Discussion of belatacept will be reserved for another review in this current issue.

Significant contributions to the development of biologics originate from European discoveries. In 1890, Emil von Behring and Shibasaburo Kitasato published their work on tetanus anti-toxin, and shortly thereafter on diphtheria anti-toxin [4]. This launched the widespread use of biologics in medicine, allowing vaccines, serum, and antitoxins to be administered for various infections. Also, at the turn of the century was Paul Ehrlich, who highlighted the need for quantifying the potency – or standardizing – this therapeutic antitoxin sera [5]. Alongside the initiatives of regulating and standardizing biologics followed the development of insulin, penicillin, and the myriad of vaccines that transformed the treatment and prevention of common diseases [5,6]. By the

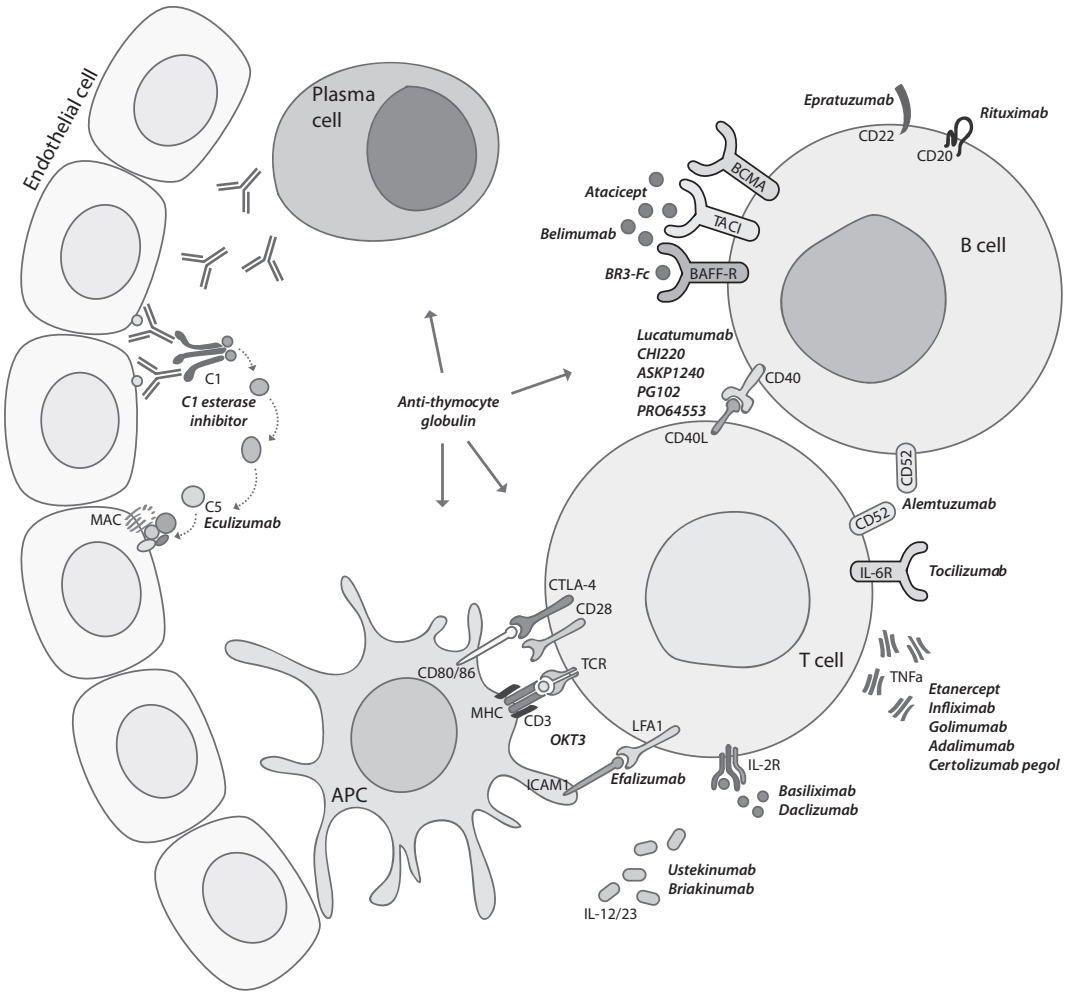

Figure 1 Clinical and preclinical biologics in organ transplantation. APC = antigen presenting cell, BAFF = B-cell activating factor, BCMA = B-cell maturation antigen, ICAM = intercellular adhesion molecule, MAC = membrane attack complex, TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

1970s, George Kohler and Cesar Milstein produced the first mouse monoclonal antibody [7]. Since the late 1990s, the European Union has approved of at least one monoclonal antibody per year (except 2002 and 2008), exemplifying the interest and promise in this therapeutic modality [3].

Biosimilar antibody development is predicted to undergo considerable growth this year, as the European Medicines Agency is re-evaluating current guidelines [8]. While target specificity makes biologics appealing, considerations must be made regarding cost, antibody stability, immunogenicity, and dose-effect standardization [6,9–12]. Furthermore, in testing safety and toxicity of novel biologics in relevant animal species (i.e. nonhuman primates and transgenic mice), biological differences across species also must be considered [13].

Biologics in clinical practice: induction agents

Allotransplantation requires immunosuppression to counter the inflammatory and allospecific immune response launched immediately after surgery [14]. Induction immunosuppression not only addresses this immediate immune activation but also may allow for a more tolerable maintenance regimen free of steroids or calcineurin inhibition [15]. In 2008, over 80% of American kidney transplant recipients received induction immunosuppression. Most were depleting agents: equine anti-thymocyte globulin (eATG – 1.5% of all recipients), rabbit ATG (44.8%), muromonab (1%), and alemtuzumab (10.7%). Basiliximab (17.8%) and daclizumab (10.9%) comprised of the remaining induction regimens [16]. In Europe, the Collaborative Transplant Study reported 38% induction

use (13% depleting, 25% nondepleting) [17]. In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) group and European Renal Best Practice Advisory Board recommended in their set of clinical guidelines for kidney transplant recipients to receive IL2R antagonists as first line induction therapy, except in patients with high immunologic risk, who are suggested to undergo lymphocyte depletion. Discussion of the agents in the following sections will be limited mainly to their uses as induction and not rescue therapies.

Depleting agents

Polyclonal anti-thymocyte globulins (ATG). Rabbit ATG (Thymoglobulin, Genzyme, Cambridge, MA, USA, indicated for treatment of acute rejection) and equine ATG (Atgam; Pfizer, New York, NY, USA) are polyclonal antithymocyte antibodies prepared from the sera of rabbits and horses immunized with human thymocytes. Such heterologous antilymphocyte sera, first described in 1899 by Mechnikov, have been used for transplantation since the 1960s [18]. Their diverse mechanisms of action include lymphocyte depletion by T-cell apoptosis and complement-dependent lysis, interference of surface, adhesion, and trafficking molecules, and induction of T-regulatory and natural killer cells [19–23]. Antibody specificities are staggeringly diverse as well, as they target immune response antigens (CD1a, CD3, CD4, CD8, CD6, CD7, CD16, CD19, CD20, CD25, CD28, CD30, CD32, CD40, CD80, CD86, CTLA-4, HLA class 1 & II, β2-M), adhesion and trafficking molecules (LFA-1, LFA-3, CD44, VLA-4, ICAM-1,2,3, CD51/61, CCR5, CCR7, CXCR4, CD56, LPAM-1), and many others (CD2, CD5, CD6, CD11b, CD29, CD38, CD40, CD45, CD95, CD126, CD138) [20–22,24–26]. This heterogeneity is likely owing to the many immune cell types present in the human thymus that are used to immunize the animals [22]. While ATG may induce immune suppression through numerous mechanisms, a prominent finding is the promotion of regulatory T cells by rATG *in vivo* and *in vitro* [27–30]. Broady *et al.* [31] recently challenged these findings by describing a transient induction of CD4 + CD25 + FoxP3 + T cells without immunosuppressive capacity after rATG exposure *in vitro*.

The ATG-Fresenius, commonly used outside of the U.S., and rATG have equivalent results for patient and graft survival [32,33]. In 1998, a multicenter, double-blinded, randomized trial found rATG to be superior to eATG in treating acute rejection [34]. Brennan *et al.* [35] also reported that a 7-day course of rATG induction compared with eATG resulted in fewer (4% vs. 25% at 1 year, $P = 0.014$) and less severe acute rejection episodes, and fewer serious adverse events including cytomegalovirus (CMV) disease (10% vs. 33%, $P = 0.025$). Ten years later, patients randomized to rATG compared with eATG induction had higher event-free survival and improved quality-adjusted life years at 10 years, without increased CMV disease or post-transplant lymphoproliferative disorder (PTLD) [36].

Today, rATG continues to be the most widely used induction agent in the US, despite the development of newer biologics. Intraoperative dosing reduces delayed graft function and hospital length of stay when compared with postoperative induction [37], which may be attributed to its role in preventing ischemia-reperfusion injury [38–42]. While historically used for high-risk patients (retransplants, extended criteria donation, or donation after cardiac death) [34,37,43–45], its use has recently been extended to living donor transplantation. Hardinger *et al.* [46] (2006) found improved 5-year patient (96% vs. 90%) and graft survival (82% vs. 79%), and lower 1-year acute rejection rate (2% vs. 21%) at their institution compared with living donor recipients nationwide.

The rATG is generally well-tolerated, but symptoms related to cytokine release, myelosuppression, and rarely serum sickness may be experienced [18,47,48]. Several studies have found increased CMV and other viral infections in rATG induction recipients compared with no induction or basiliximab [49–51]. While the data for increased risk of PTLD with rATG are mixed [52–56], our understanding of Epstein Barr viral (EBV) infection, patient characteristics, and types of combination immunosuppression may help identify patients at higher risk for malignancies [57–61].

Muromonab-CD3 (Orthoclone OKT3; Janssen-Cilag), the first monoclonal antibody in clinical medicine, is a murine IgG2 monoclonal antibody binding to the CD3ε antigen and therefore to the CD3 complex on mature T lymphocytes [62]. Its mechanism of action involves disruption of T-cell receptor (TCR) binding, internalization of OKT3-CD3/TCR complex, complement-mediated cell lysis, and resultant T-cell depletion [47,63]. Muromonab was approved for use in 1986 after demonstrating superior rejection reversal rate (94% vs. 75%, $P = 0.009$) and 1 year graft survival (62% vs. 45%, $P = 0.029$) over conventional corticosteroid therapy [64–66].

Although, an effective induction agent as well [67–71], muromonab carries a significant side effect profile, which includes cytokine release syndrome secondary to its mitogenic properties [72–79], pulmonary edema [80,81], aseptic meningitis [82], and EBV related PTLD [54,83]. In addition, up to 80–85% of patients develop antimurine antibodies that may neutralize the drug and its immunosuppressive effects [65,84–86]. Side effects may be mitigated with steroid premedication [72,87–89]; nevertheless, manufacturer Janssen-Cilag announced the

discontinuation of muromonab production in January 2010 [48]. A well-tolerated substitute for muromonab, A1-CD3, was prepared in Prague and offered to 19 renal allograft recipients [90]; this therapy was not further developed for general clinical use.

Alemtuzumab (Campath-1H) is a humanized IgG1 monoclonal antibody targeting the surface molecule CD52, a membrane glycoprotein densely distributed on T and B lymphocytes (450 000 molecules per cell), natural killer cells, and less so on monocytes, macrophages, and eosinophils. By complement activation and antibody-dependent cellular cytotoxicity, alemtuzumab induces profound and sustained lymphopenia (50% T cell recovery at 36 months [91]). Macrophages, natural killer cells, and B cells may reconstitute to normal levels as rapidly as 1–3 months [92].

Early studies confirmed its efficacy as an induction agent [93–96], including ours from the University of Wisconsin where renal transplant patients receiving Campath-1H experienced overall less rejection ($P = 0.04$), less rejection ($P = 0.01$) and improved graft survival ($P = 0.12$) among patients with delayed graft function, and no difference in infection or malignancies when compared with basiliximab, daclizumab, rATG, and muromonab [97]. In May 2011, Hanaway *et al.* presented a multicenter, randomized, prospective trial of renal transplant recipients assigned to alemtuzumab versus basiliximab in low-risk and versus rATG in high-risk stratification (retransplant, PRA > 20%, or black race). Alemtuzumab induction resulted in significantly fewer biopsy-confirmed acute rejection rates at 6 and 12 months for both risk groups, and fewer 3-year rejection rates among low-risk patients [98]. In comparison with rATG, alemtuzumab showed mixed results in kidney and kidney-pancreas transplants, with equivalent or decreased acute rejection rates seen with alemtuzumab [99–103]. Alemtuzumab does confer a significant cost benefit, as a course of rATG cost over 400% more than a single dose of alemtuzumab in 2005 [99].

Alemtuzumab has been associated with a rapid reconstitution of memory T-cells [104,105]. Early B-cell reconstitution to greater than pretreatment levels with a concurrent surge in serum B-cell activating factor (BAFF) levels has also been described [106,107]. Alemtuzumab and sirolimus treated patients experienced a higher incidence of antibody mediated rejection, with 42% developing HLA antibodies [95,108]; fewer humoral rejection events were observed when alemtuzumab was combined with other agents, especially calcineurin-inhibitors [97,109]. When used alone, alemtuzumab was associated with a 100% incidence of rejection with weeks, proving that depletion alone does not induce tolerance in humans [110].

In summary, Alemtuzumab effectively prevents early T-cell mediated rejection and may play a growing role in prophylaxis of acute rejection. The combination of Belatacept and depletion with Alemtuzumab appears to be highly immunosuppressive yet safe in humans [110], reducing the risk of antibody-mediated rejection seen in other calcineurin inhibitor-free protocols.

IL2Rα (CD25) blockade

Interleuking-2 receptor α chain (CD25) enhances binding of IL2 to the receptor complex, augmenting lymphocyte activation and proliferation [111]. Two monoclonal antibodies targeting IL2Rα and thus inhibiting IL-2 mediated lymphocyte activation/proliferation are used for induction immunosuppression: basiliximab (Simulect, Novartis) is a recombinant chimeric mouse/human IgG1 monoclonal antibody, and daclizumab (Zenapax, Hoffmann-La Roche) a humanized monoclonal antibody. Anti-IL2R antibodies reduce the risk of acute rejection without increasing the incidence of adverse effects, namely CMV infection and malignancy [48,54,112]. While their efficacy in immunoprophylaxis compared with thymoglobulin is debatable as discussed above, their tolerability and safety profile make IL2R blockade attractive for induction. No significant difference between the two agents has been found [113,114]; however, daclizumab was discontinued in 2009 and is no longer available for clinical use.

The IL2R antagonists increasingly have been employed for induction immunosuppression. In 2009, 92% of kidney recipients in Australia received IL2R blockade (ANZDATA Registry, Annual Report 2010). While IL2R antagonists have a more tolerable side effect profile, studies have demonstrated reduced incidence and severity of acute rejection in high-risk patients receiving thymoglobulin induction over basiliximab [115,116]. Five-year follow-up by Brennan and Schnitzler revealed lower rates of acute rejection, graft loss, and death with thymoglobulin compared with basiliximab (37% vs. 51%, $P = 0.04$) [117]. Others have found comparable outcomes between the two induction agents [118–120].

Biologics in clinical development: costimulation blockade

As the CD28/CD80/CD86 pathway will be well described in the review of Belatacept, here we will focus on the CD40/CD154 pathway and its role in organ transplantation. CD40 is a molecule constitutively expressed on surface of B cells, dendritic cells (DC), and macrophages. When these cells present antigen to T cells, signaling through CD40 after its activation by CD154 results in B-cell activation, DC maturation, and increased production of pro-inflammatory cytokines. CD154, however, is rapidly induced on the surface of T cells after the activation of the

TCR. Thus, CD40/CD154 provides an attractive target for immunosuppressive therapies for both the constitutive nature of expression of CD40 on APC's and the activation specific expression of CD154 on T cells [121,122].

Early studies in mouse models first published by the groups of Larsen and Hancock demonstrated that blockade of CD154 could result in prolonged but not indefinite allograft survival. Long-term acceptance of allografts, however, required additional immunosuppressive therapies [123–125]. Follow-up studies in nonhuman primate models demonstrated similar results. The groups of Kirk and Knechtle found that blockade of CD154 prevented allograft rejection in nonhuman primates but unfortunately did not provide indefinite graft survival [126,127]. Based on these results, development of humanized anti-CD154 antibodies for clinical use moved forward. However, progress stalled when clinical and nonhuman primate trials demonstrated that blockade of CD154 was associated with thromboembolic complications [128].

Recent developments of humanized, nondepleting, anti-CD40 antibodies have renewed interest in blockade of this costimulation pathway [129]. Humanized anti-CD40 antibodies have been able to prevent acute rejection and prolong renal and islet allograft survival in nonhuman primate models of transplantation. In addition, these anti-CD40 antibodies appear to be safe and effective as maintenance immunosuppressive therapy as well [129,130]. These discoveries would suggest that co-stimulation blockade of the CD40/CD154 pathway is still viable as an immunosuppressive strategy and may potentially benefit patients undergoing organ transplantation. Monoclonal antibodies to CD40 include lucatumumab, Chi220, ASKP1240, PG102, and PRO64553 [131].

Biologics in clinical development: B cell therapeutics

The detrimental impact of alloantibodies on long-term allograft function and survival has been well documented over the last decade [132–134]. As such, several antibodies and small molecules have emerged in the transplant setting, targeting $CD20^+$ B cells, BAFF, and complement components. Currently, rituximab has shown most promise in sensitized patients among B-cell therapeutics, but data supporting the clinical use of these biologics in transplantation are incomplete. We believe that evaluation of their use in high-risk patients in a rigorously controlled study will provide valuable information. Objective comparison of the new immunosuppressive agents will depend on the ability to conduct clinical trials involving multiple agents that are owned by different companies. Unless public support is available, such comparative trials may not readily occur.

B cell depletion

Rituximab (Rituxan; IDEC Pharmaceuticals) is a mouse/human chimeric IgG1 monoclonal antibody to CD20. It induces B-cell depletion through antibody and complement dependent cytotoxicity and apoptosis, primarily in peripheral blood [135]. In the spleen, it preferentially depletes naïve B cells but not memory B or plasma cells [136]. Similarly, *in vitro*, naïve B cell (CD19+CD27−) but not memory B cell (CD19+CD27+) proliferation is inhibited [137].

Rituximab was introduced in the early 1990s to the transplant field as a therapy for PTLD [138,139]. Its main successes in transplantation involve its use for ABO incompatible transplants and desensitization. Genberg *et al.* presented 3-year results for pediatric and adult kidney patients receiving ABO incompatible versus compatible living donor transplants. Twenty ABO incompatible patients received a single dose of rituximab day -30, oral immunosuppressants day starting day -10, and intravenous immunoglobulin on day -1; no difference in patient or graft survival, acute rejection, nor infectious complications were observed [140]. In 2011, Fuchinoue reported 5-year outcomes of living related recipients that were ABO compatible ($n = 280$), ABO-incompatible with splenectomy ($n = 63$), or ABO-incompatible with rituximab induction ($n = 50$), concluding that ABO incompatible recipients undergoing rituximab induction had 100% graft survival at 5 years with equivalent risk of antibody-mediated rejection and CMV infection as the other groups [141]. Vo *et al.* shared their desensitization experience using rituximab and intravenous immunoglobulin in 20 highly sensitized patients, where 100% and 94% 12-month patient and graft survival rates were achieved with no serious adverse events [142]. When used as rescue therapy for antibody-mediated rejection, 22 patients treated with rituximab and plasmapheresis had 77% graft survival at median 9 months but a high incidence of serious infections (86%) [143]. Epratuzumab (Immunomedics/UCB), a humanized IgG1 monoclonal antibody to CD22 in phase III trials for lupus, improves the efficacy of rituximab when given as combination therapy for lymphoma [144], and may be a promising target for alloimmunity as well.

BAFF blockade

The BAFF, also known as B Lymphocyte Stimulator (BLyS), TALL-1, THANK, and zTNF4, is a member of the tumor necrosis factor cytokine family expressed mainly on T cells and dendritic cells for B-cell costimulation [145,146]. BAFF binds to receptors BCMA (B cell maturation antigen), TACI (transmembrane activator), and BAFF-R (BAFF receptor) for B cell survival, proliferation, and maturation. Initially studied in autoimmune disease,

its role in transplantation has been described in chronic graft-versus-host disease and correlation with donor specific HLA antibodies, diminishing graft function, higher panel reactive antibodies, B-cell reconstitution, and C4d+ allograft rejection in kidney recipients [147–151].

Belimumab (Benlysta; Human Genome Sciences/GlaxoSmithKline) is a fully human recombinant IgG1 monoclonal antibody to BAFF, FDA approved in March 2011 for SLE. Mustafa *et al.*, in a murine cardiac allograft model, found that treatment with anti-BAFF mAB depleted follicular (B220+IgM+CD21/35+) and alloreactive B cells and abrogated the alloantibody response, compared with untreated controls [152]. The same group is enrolling patients in a phase II clinical trial of desensitization with belimumab in sensitized patients awaiting kidney transplantation (clinicaltrials.gov).

Atacicept (ZymoGenetics/Merck Serono) is a recombinant Fc fusion protein, composed of the extracellular portion of the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) receptor and the Fc portion of human IgG1. It neutralizes BAFF and its sister ligand APRIL (a proliferation-inducing ligand), and has been evaluated in rheumatoid arthritis, SLE, multiple sclerosis, and B-cell malignancies [153]. In cynomolgus macaques, atacicept only modestly reduced peripheral B cells by 20%, but in combination with rituximab induced greater (near-complete) B-cell depletion in lymphoid tissues than either drug alone. In addition, significant reduction of serum Ig was induced with atacicept with or without rituximab [153]. In allosensitized nonhuman primates, atacicept reduced T-cell and B-cell alloantibodies by 36% and 24%, respectively [154]. Atacicept is in phase II/III clinical trials for SLE and has yet to be evaluated in human transplant patients. It has failed to show efficacy in clinical trials for rheumatoid arthritis and multiple sclerosis [155,156].

The BR3-Fc (Briobacept, Genentech/Biogen Idec, discontinued in 2011) is a recombinant homodimeric fusion protein made of the extracellular domain of human BR3, also known as BAFF-R, and the Fc portion of human IgG1. In cynomolgus macaques, BR3-Fc induced 45–60% peripheral B-cell reduction in a dose-independent manner, mostly of naïve (CD21+CD27−) B cells; significant reduction of naïve and memory (CD21+CD27+) B cells was noted in secondary lymphoid organs. Additional analysis with immunohistochemistry revealed decreased follicular, marginal, and mantle zone B cells [157].

Complement blockade

Complement fixing actions of antibodies are well known, and complement deposition (i.e. C4d) in histologic preparations is often used in the diagnosis of antibody-mediated rejection. In addition, elevated levels of urine C5a and plasma levels of C1rsC1-inhibitor complexes have been detected in acute renal allograft rejection [158,159].

Eculizumab (Soliris, Alexion) is a recombinant humanized IgG2/4 monoclonal antibody to complement protein C5, FDA approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Stegall *et al.* compared post-transplant eculizumab versus pre-operative plasma exchange (control) in patients with pretransplant B flow cytometric crossmatch channel shifts between 200 and 450. Incidence of antibody-mediated rejection within 3 months was 7.7% for eculizumab recipients compared to 41% for controls ($P = 0.0031$); however, a high number of patients developed donor specific antibodies by 3 months (50% eculizumab vs. 43% control, $P = 0.63$) [160]. Case reports have demonstrated effective rescue treatment of severe complement activation and antibody-mediated rejection by eculizumab in an ABO-incompatible kidney-pancreas transplant and a re-transplanted kidney recipient [161,162].

The C1 esterase inhibitor (Berinert, Aventis-Behring) is a plasma-derived human C1 esterase inhibitor, FDA approved for the treatment of hereditary angioedema. Its use in allotransplantation has primarily been dedicated to tissue protection from ischemia/reperfusion injury [163]. In a case study from 1997, a 19-year-old O-typed boy accidentally received a B-typed heart transplant and underwent an assortment of therapies, including plasma exchange, extracorporeal immunoabsorption, intravenous immunoglobulins, and C1 inhibition. While inadequate maintenance immunosuppression necessitated total lymphoid irradiation for 2 months, the patient stabilized and was doing well at 42 months. Early successes were attributed to complement inhibition [164]. C1 inhibition in animal models of xenotransplantation has demonstrated tissue protection by reducing complement deposition and destruction in hyperacute rejection [163].

Biologics in clinical development: anti-adhesion and anti-cytokine approaches

Efalizumab (Raptiva, Genentech/Merck Serono) is a humanized monoclonal antibody to the CD11a subunit of the leukocyte function antigen (LFA-1) pathway, thereby disrupting lymphocyte adhesion and migration into tissues. In an islet cell transplantation trial, Turgeon *et al.* compared a group receiving an efalizumab-based protocol (daclizumab, mycophenolate mofetil, efalizumab, with tacrolimus taper) versus the Edmonton protocol (daclizumab, tacrolimus, and sirolimus). Efalizumab-treated patients experienced fewer immunosuppression related events and none required repeat islet infusion to achieve insulin independence. Efalizumab was withdrawn from

the market in 2009 owing to risk of progressive multifocal leukoencephalopathy; patients whose efalizumab in the above study was discontinued shortly experienced islet dysfunction, suggesting efficacy of the drug [165]. Posselt *et al.* achieved similar outcomes in a calcineurin inhibitor-free regimen, using ATG induction with efalizumab and sirolimus or mycophenolate; tacrolimus replaced efalizumab after the drug was withdrawn. All patients achieved insulin independence, half after a single transplant, without serious adverse events [166]. Interestingly, all patients were found to have a significant, persistent increase in CD25hi and CD127lo CD4 + FoxP3 + regulatory T cells out to 1 year.

Serum and urine biomarkers for acute allograft rejection clearly demonstrate the presence and impact of cytokines in the rejection process [167,168]. In addition to IL2R blockade as described above, therapeutic targeting of other cytokines may provide important immune suppression in induction and rescue settings. Ustekinumab (Stelara, Centocor) is a human IgG1 monoclonal antibody to the p40 subunit of interleukins 12 and 23, cytokines involved in T-cell differentiation into Th1 and Th17 phenotypes [169]. A similar antibody is Briakinumab, which is currently in phase III studies for the treatment of psoriasis [170]. Tocilizumab (RoActemra or Actemra, Roche/Genentech/Chugai) is a recombinant humanized IgG1 monoclonal antibody to interleukin 6 receptor, developed for rheumatoid arthritis. IL6R promotes T-cell activation and B-cell differentiation among other pleiotropic effects [171], making it an attractive candidate for use in transplantation.

Proinflammatory cytokine tumor necrosis factor (TNF) alpha is elevated in the serum of acutely rejecting patients [172]. Hu *et al.* conducted a meta-analysis of TNF-A-308G/A polymorphisms and found an increased risk of acute rejection in renal allografts with donor and recipient TNF2 allele positive genotypes. Thus, TNFa blockade may also emerge as an adjunct therapeutic. Etanercept (Enbrel, Amgen/Pfizer), a fusion protein of TNF receptor 2 with human IgG1, combined with exenatide improved engraftment and long-term survival in patients undergoing supplemental islet infusions [173]. FDA approved anti-TNF antibodies include chimeric IgG1 infliximab (Remicade), human IgG1 golimumab (Simponi), pegylated humanized Fab certolizumab pegol (Cimzia), and human IgG1 adalimumab (Humira) [170].

Conclusion

The deluge of novel biologic agents entering clinical trials has yielded several that may be promising for immunomodulation in transplantation. These therapies may help us identify a better solution to steroid-refractory rejection, chronic allograft loss, transplantation in highly sensitized recipients, avoidance of calcineurin inhibition, and rescue immunosuppression, among others. While individual agents may be insufficient for tolerance induction, the ability to target specific pathways may allow for highly customized treatment.

Authorship

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