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Glomerulonephritis – Do We Have Promising Role of Monoclonal Antibodies?

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Abstract

In present era, drugs like steroids, cytotoxic drugs and calcineurin inhibitors are the backbone to treat immune mediated glomerular diseases. Failure of these therapies often results in persistence of proteinuria, refractory illness and later chronic kidney diseases. The quests to find an answer to such diseases have resulted in the introduction of monoclonal antibodies or target specific drugs. Rituximab is the first monoclonal antibody, which was studied extensively in pauci-immune glomerulonephritis and is now approved for its role in refractory and new onset renal vasculitis. Belimumab has shown role in active systemic lupus erythematosus (SLE). With increasing insight in glomerular pathophysiology, many new monoclonal antibodies are now being under trial. Their encouraging results allowed further research on target cytokines, inflammatory mediators and different lymphocyte populations. This review shall discuss monoclonal and their emerging role in glomerulonephritis.

Keywords: Monoclonal antibody; Proteinuria; Vasculitis; Glomerulonephritis

Introduction

Monoclonal antibodies can target immune mechanism either at antigen presenting cell, T-cell or B-cell pathway, complement system, co-stimulatory molecule or as an anticytokine therapy. Paul Ehrlich and Elie Metchnikoff were first one to give this idea of target molecule and received Nobel Prize in 1908 for their work on immunity and target immune mechanism [1]. Kohler and Milstein discovered the first monoclonal antibody against B-cell line in mice in 1975 and shared Nobel prize for physiology of medicine in 1984 [2]. Since the generation of first molecule and their magic role in malignancy, there is a rapid advancement in both number of monoclonal drugs and their trials for testing efficacy in other diseases. Glomerulonephritis (GN) is indeed one such diseases, where to prevent progression to chronicity, monoclonal drugs were used and showed significant improvement. OKT3 was the first monoclonal drug used in

kidney transplant rejection and then numbers of monoclonal were introduced in transplantation. Subsequently these were then introduced in glomerulonephritis and showed their efficacy. This review shall focus update on exclusive role of monoclonal drugs, trials to clinical usage in glomerulonephritis.

Rituximab

In GN, rituximab is the first extensively used and successful monoclonal drug. It is now approved for ANCA vasculitis. It is a murine-human chimeric genetically engineered monoclonal antibody against CD20, an immature and mature B cells surface marker, which is not expressed on plasma cells. Drug contains human IgG1 in the constant region (Fc) and murine heavy and light chain in variable regions (Fab).

It has an anti CD-20 action which is recognized as calcium channel blocking action and thus mediates apoptosis by blocking intracellular signaling and altering kinases activity [3]. It induces cell lysis through complement-dependent and independent mechanisms and also has direct target action against podocytes which is independent of its B-cell action [4,5]. Here it binds to sphingomyelin phosphodiesterase acid-like 3b protein (SMPDL-3b) and regulates acid sphingomyelinase activity to prevent protein disruption of the actin cytoskeleton and podocyte apoptosis.

Rituximab in ANCA Vasculitis

Rituximab is now FDA approved drug for vasculitis.

Till date guidelines recommends cyclophosphamide as the first line therapy for crescentic small vessel pauciimmune ANCA vasculitis, which is there for more than four decades now. With the success of multiple case reports, randomized trial were conducted which showed it as non-inferior and safer to cyclophosphamide, when used as an induction therapy. It has

Even showed superior results as compared to azathioprine when used as maintenance drug. Here below discussing briefly the results of these landmark studies which began new era for rituximab in ANCA vasculitis.

Rituxivas study

Included 44 patients of new onset ANCA associated renal vasculitis. Rituximab on day 0,7,14 and 21 was given with 2 doses of cyclophosphamide on day 0 and 14 in induction and compared with IV CYP and prednisolone therapy. No maintenance therapy was used. Results showed sustained remission of 76% in rituximab versus 82% in cyclophosphamide group at one year. No significant difference in the outcome of two therapies was noted [6].

Clinical usage

1. A dose of 375/m²/intravenous infusion once weekly for 2-4 weeks. Dosage up to 1 g/infusion used.
2. Premedication with acetaminophen, antihistamine and steroid.
3. PCP prophylaxis for 3 months Drug Infusion requires preparation in normal saline (NS dilution half of dose strength) Initial rate of infusion is 50 mg/hour, which in the absence of infusion toxicity increases to 50 mg/hour every 30 minutes. (Recommended by manufacturer with the maximum rate of 400 mg/hour).
4. Monitoring advised with serum level of lymphocyte counts, proteinuria, circulating B cells (CD19<1%), B cell recovery is usually detectable by 6 to 9 months.
5. Available in 100 mg/10 ml and 500 mg/50 ml strength.
6. Infusion related allergic reactions can be seen with first infusion, varying from mild fever, chills, headache and nausea to severe bronchospasm, hypotension and angioedema. Rarely severe muco-cutaneous reactions, ARDS, myocardial ischemia and arrhythmias.

Rave trial

RCT included 197 patients of new onset or relapsed ANCA associated vasculitis. Renal involvement was seen in 66% of enrolled patients. A weekly 4 dose of rituximab was compared with oral cyclophosphamide in induction and in maintenance no therapy in rituximab versus azathioprine in CYP group was compared. 64% in rituximab and 53% in cyclophosphamide group at 6 months achieved remission and subsequent remission in two groups seen at 12 and 18 months were 48 vs. 39% and 39 vs. 33% respectively. In relapsing disease 67% vs. 42% remission in rituximab and cyclophosphamide group at 12 month were documented respectively and suggested better outcome [7].

Mainritsan trial

French vasculitis group compared rituximab and azathioprine in the maintenance phase when the induction therapy used for two groups were cyclophosphamide and steroids. 118 patients were enrolled, 70% had renal involvement. Rituximab was given on day 0, 14 and 3 doses at 6 monthly intervals. At 28 months, 29% relapses seen in azathioprine while 5% in rituximab group while both group had similar rates of adverse events [8]. A retrospective analysis of 172 patients with ANCA vasculitis

suggested successful remission on maintenance rituximab therapy every 4 monthly for 7 year [9].

In eosinophilic granulomatous polyangiitis, available limited data suggests good efficacy in achieving remission [10,11]. Further studies required establishing recommendations here.

Recommendations

KDIGO guidelines 2012, recommend (For Wegner granulomatous, microscopic polyangiitis) rituximab therapy as an:

1. Alternative second line induction therapy in necrotizing GN.
2. Alternative therapy in resistant and progressive diseases along with other options [12].

EULAR/EDTA Guidelines 2015 for ANCA vasculitis:

1. Best response in wegnesrgranulomatosis, microscopic polyangiitis then eosinophilic granulomatous polyangiitis.
2. For remission-induction of new-onset organ threatening or life-threatening or relapsing AAV.
3. Recommend treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab.
4. Rituximab also recommended as an alternative in maintenance therapy [13].

Rituximab in Lupus Nephritis

Role of rituximab trial came with failure of the first line therapies in biopsy-proven active Class III, IV and V lupus nephritis (LN) as per International Society of Nephrology/Renal Pathology Society (ISN/RPS). Persistence of high activity is indicated clinically by microscopic hematuria, proteinuria and rise in creatinine and histo-pathologically by glomerular hypercellularity, cellular crescents, leukocytes infiltration, wire loops, fibrinoid necrosis and tubular mono-nuclear infiltration.

Despite initial reports of successful usage of rituximab in lupus nephritis, controversies still exists on its efficacy here. Both EXPLOR (for moderate to severe SLE) and LUNAR study (for Lupus nephritis) was expected to come with favorable outcome but results did not favor the primary outcome [14-16].

Lunar

RCT phase III trials enrolled 144 patients with class III or class IV LN to receive rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182. The primary end point was renal response outcome at week 52. (Complete and partial) renal response rates were 45.8% in placebo and 56.9% in receiving rituximab group (P=0.18). Rate of serious adverse events, including infections, were similar in both groups (placebo versus rituximab) but neutropenia, leukopenia, and hypotension occurred more frequently in the rituximab group. Contrary to LUNAR trial, extended report of prospective observational study RITUXILUP (Rituximab and Mycophenolate mofetil without Oral Steroids for Lupus Nephritis) suggested successful outcome with complete and partial remission in 45/50 patients, relapses

in 11/50 and systemic flare in 6 patients over follow up of 65 weeks [17].

Another report in favor of rituximab role in refractory LN came from systematic analysis by Weidenbusch et al. involving 300 patients with a mean follow-up of 60 weeks in 26 studies. Both complete and partial remission was seen in 87% of patients with LN class III, 76% with class IV and 67% with Class V while complete responses alone was seen in 60%, 45%, 40% and 24% of class III, IV, V and mixed respectively in refractory lupus [18]. Dilemma still exists for its role and future trial may provide the definitive answer here [19].

RING: "Rituximab for Lupus Nephritis with Remission as a Goal" Clinical Trials.gov NCT01673295

Recommendations

1. KDIGO 2012 lupus nephritis [12].
2. In resistant lupus nephritis with either of other alternatives option like IgG.
3. ACR guidelines [18].
4. Rituximab –an alternative for resistant and refractory lupus nephritis

Rituximab in anti-GBM

No definitive data available. Disease often presents as rapidly progressive crescentic glomerulonephritis and if not respond to plasmapheresis and first line immunosuppressive treatment then progress to chronic kidney diseases. Case reports have shown successful outcome of B-cell therapy in refractory illness in term of disease activity but had no effect on improvement in GFR [19-21].

Rituximab in membrano-proliferative GN

Pilot study by Dillon et al. showed some benefit of Rituximab in type 1 MPGN. 2/6 had complete remission and 3/6 had partial remission and mean time to achieve remission was 6-9 month [22]. Case series, and RCT in mixed cryoglobulinemia (MC) have shown significant improvement in proteinuria [23,24]. Multicenter study retrospectively evaluated the effects of rituximab in 87 patients with active MC and 38/87 with Nephropathy. 92% had association with HCV. 95% showed significant improvement in proteinuria and 50% had complete remission [25]. In study of 93 patients by Saadoun et al. pegylated-interferon- α /ribavirin with rituximab was compared with Peg-IFN- α /Rbv alone. Clinical remission was achieved earlier in ritux group (5 vs. 8 months) and significant difference in renal response rates (80 vs.40%) [26].

Recommendation

KDIGO [2D] suggest use of rituximab or other alternative for patients with HCV and mixed cryoglobulinemia (IgG/IgM) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia.

Rituximab in IgA nephropathy

1. No defined role till date. STOP- IgA study -an open label
2. RCT failed to show any benefit by adding rituximab [27,28].

Belimumab

Approved by the Food and Drug Administration in 2011 for the treatment of active SLE but not for severe CNS lupus and severe nephritis. It is a human IgG1 λ monoclonal antibody with elimination half-life of 19.4 days. Onset of action for B cell suppression is 8 weeks, with clinical manifestations improvement seen in 16 weeks [29]. Drug act by binding to the soluble form of B-lymphocyte stimulator (BlyS), which is a TNF superfamily ligand and thus block autoantibodies. It acts in the bone marrow and block plasma cell, which in turn inhibit prolonged antibody memory. It blocks intracellular signaling cascade through all three BlyS-binding receptors (trans membrane activator and CAML (calcium modulating cyclophilin ligand) interactor (TACI), BCMA and BAFF-R and finally B cell proliferation. Belimumab also blocks T cell secretion of interferon-gamma (INF- γ), interleukin-2 (IL-2) [IL-2-dependent proliferation of T cells and antibody production] and also transition of immature B cells from the T1 to T2 stage thus preventing mature B cells formation in spleen [30].

Clinical usage

Dosage: 10 mg/kg IV injection on Days 0, 14 and 28, and then every 4 weeks. For infusion, dilution in 250 ml 0.9% normal saline and administration in 1 hour. Premedication prophylaxis with anti-allergic, anti-inflammatory and hydrocortisone is recommended Monitoring with SLE activity markers.

Benalysta: 120/1.5 ml and 400 mg/4.8 ml sterile water to make a concentration of 80 mg/ml. Costs of \$443 for 120 mg and \$1,477 for 400 mg vial. Infusion related reactions common. Especially with concomitant administration of mycophenolatemofetil. More than 5% reported nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

Belimumab in lupus erythromatosus

Randomized double blind controlled trial in phase III now have shown its efficacy in lupus activity [31,32]. In BLISS-52, 865 patients' were enrolled and efficacy was analyzed at week 52. 58% vs.44% remission rate seen with belimumab and placebo respectively.

BLISS-76, 819 SLE patients were analyzed at week 52 and then at week 76 and reduced disease activity was noted 43% and 34% respectively. Efficacy noted at week 76 was not statistically significant. In future, results of two new trials in SLE patients with nephritis may give definitive role of Belimumab in lupus nephritis and change present treatment guidelines. The two trials are currently recruiting lupus nephritis patients. NCT02260934: (CALIBRATE STUDY) Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis (ITN055AI). NCT01639339: (BLISS-LN): Efficacy

and Safety of Belimumab in Patients With Active Lupus Nephritis. Other than SLE nephritis, Belimumab is now being evaluated for the treatment in ANCA vasculitis (BREVAS study, NCT01663623).

Recommendation

Belimumab: FDA approval for SLE but no recommendation for active CNS lupus and lupus nephritis.

Eculizumab

It is a long-acting humanized monoclonal IgG2/4 κ antibody against complement C5. Half-life approximately 11 ± 3 days and is mainly distributed in the vascular space. It binds to complement C5 and prevent its breakdown into C5a and C5b by C5 convertase. In activated complement pathway, complement C5a increases the permeability of blood vessels and attracts inflammatory cells by chemo-taxis while C5b binds to other complement components (C6, C7 and C8) to form the MAC (membrane attack complex) [33,34]. MAC has role in killing the microorganism especially Neisseria. First successful role came in paroxysmal nocturnal hemoglobinuria and now approved for atypical HUS [35].

Eculizumab in complement mediated glomerulonephritis and aHUS

C3 glomerulopathy is recently coined term for the disease process due to abnormal activation of complement pathway. It is further classified into dense deposit disease (DDD) and C3 glomerulonephritis. Understanding pathophysiology and complement activation is beyond the scope of this review but after knowing this complex physiology of complement system activation and its approval in aHUS, multiple cases were reported for its role in MPGN [36,37]. Both beneficial as well as failure reports came out and also successful withdrawal from dialysis after drug initiation reported [38-40]. Bombardieri et al. demonstrated successful outcome of Eculizumab in six patients (three patients each with dense deposit disease and C3 glomerulonephritis) in term of proteinuria and improved renal profile. Even repeat renal biopsy after 1 year suggest less activity with no evidence of endocapillary proliferation [41]. Currently two open label studies in phase I (NCT01221181) and phase II (NCT02093533) are undergoing and their outcome shall provide further information regarding efficacy and timing of initiation [42].

Eculizumab in Atypical Hemolytic uremic syndrome

Characterized by activation of complement mediated hemolysis and renal syndrome. Eculizumab is FDA approved for aHUS. Multi-centric study in phase II has reported its efficacy in aHUS [43,44]. Phase II study in trial 1, enrolled 17 patients with progressing thrombotic microangiopathy (TMA). Hematologic normalization was achieved in 76% at 26 weeks and 88% at 1 year. Complete TMA response was achieved by 65% at week 26 and 76% at the 1 and 2-year. 88% had TMA free events. Trial II, in phase II study, 20 patients with long duration of aHUS and chronic kidney disease were enrolled. TMA free events achieved

at 26 weeks 1 and 2 year were 80%, 85% and 95% respectively. 18 patients (90%) achieved and maintained hematological remission. Complete TMA response was achieved in 25% at 26 weeks, 35% at 1 year, and 55% at the 2 year. None of the patients in study had meningococcal infection and no graft loss seen in renal transplant patient with eculizumab therapy. Previously, French study group reviewed and summarized case reports of 24 patients including 11 children, where eculizumab was used as a curative therapy in native kidneys (n=14) or transplanted kidneys with HUS (n=10). Among these 24 patients, 15 (62.5%) were found to have complement mutations, mostly in CFH (10/24, 42%). Excellent outcome was noted in both pediatric and adult patients [45]. Another aHUS report gave some hope in deciding duration and cost burden of therapy where drug was discontinued for 95 months in 10 patients who had achieved stable remission. In this report 3 patients relapsed within 6 weeks of stopping therapy. 7/10 did well and no other adverse effect noted [46].

Clinical usage

1. Dose variable as per weight (10-40 kg and more) 300 to 900 mg per week for 1-4 weeks then 300-1200 mg every 2-3 weeks.
2. Infusion 300 mg/30 ml in 30 ml dilution (NS/ Dextrose 5%, ringer lactate) and transfuse over 35 min.
3. Monitoring with HUS activity markers for 8-12 weeks if stopped.
4. Meningococcal vaccination 2 weeks prior is recommended
5. Soliris : 10 mg/ml solution for intravenous infusion. Available strength: 30 ml /300 mg single use vial. Cost is \$6830 per 300 mg vial.
6. Risk of meningococcal infection, and serious infections due to Streptococcus pneumoniae and H. influenzae type b (Hib). Prior vaccines are recommended.
7. No infusion related reactions noted.
8. Adverse effects (<15%) in trial. Include hypertension, URTI, diarrhea, headache, anemia, vomiting, nausea, UTI and leukopenia. Acceleration of hepatotoxicity.

Brief on other monoclonal antibodies

Multiple monoclonals have been introduced in immune mediated glomerular disease. Action on specific target receptors, make them more specific with less side effects compared to previous available therapies. Target receptor can be at T cell (Alemtuzumab, Basiliximab), B-cell (Epratuzumab, Belimumab), Anti-cytokine (infliximab, adalimumab), complement (CCX168) and co stimulation (Abatacept, belatacept) pathway. Few with successful efficacy in GN have been discussed above. Many other monoclonal antibodies were studied in nephritis and a long list of monoclonal failed to show benefit. ACCESS study reported that abatacept/CTLA4-Ig (Cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin fusion protein) plus low dose intravenous cyclophosphamide followed by azathioprine did not improve remission rates in patients with lupus nephritis [47]. Small open label trial assessed

the safety and efficacy of abatacept as a remission therapy in patients with relapsing, non severe GPA did not provide statistical significant result [48]. A phase III, multicenter RCT to assess the efficacy of abatacept to permit steroid free remission in relapsing GPA is underway. Abatacept is an inhibitor of the T-cell co-stimulatory signaling molecule B7-1 (CD80) and CD86 that are present on the surface of B cells, dendritic cells, and macrophages. Ocrelizumab, anti CD-20 failed show significant much benefit in Lupus nephritis and trials terminated due to association with very high rate of infection [49]. Anti-IL6 and IL-6R are now being tested in lupus nephritis. A phase II trial of sirukumab (an antiIL6 monoclonal antibody) in lupus nephritis reported negative findings, with a high incidence of infectious complications [50]. A small study of tocilizumab (an antiIL6R monoclonal antibody) in SLE nephritis yet to give result. Anti-cytokine therapy, certolizumab, pegol, and golimumab have yet to show their effect in vasculitis. Mepolizumab is an antiIL5 monoclonal antibody that according to case reports showed favorable response in patients with EGPA [51,52]. Two RCTs are assessing the efficacy of mepolizumab induced remission and steroid sparing capacity in EGPA [53,55]. Omalizumab- an antiIgE monoclonal antibody that prevents IgE binding to Fcε receptors on mast cells, studied in case series but yet show its definitive results in EGPA [56]. Apart from glomerulonephritis, monoclonals have been used extensively in kidney transplantation and nephrotic syndrome. Rituximab has successful outcome in calcineurin dependent, membranous nephropathy, steroid dependent Nephrotic syndrome. Also Other monoclonals like Abatacept, Fresolimumab (an IgG4 humanized Monoclonal antibody against all three isoforms of TGF-β), Adalimumab (human monoclonal IgG antibody against tumor necrosis factor α (TNF-α) have shown significant reduction in proteinuria and given some hope in FONT (First portion of novel therapies) study for focal segmental glomerulosclerosis [57].

Recommendation

Eculizumab: FDA approval for aHUS but yet to see definite outcome and recommendations in C3 glomerulopathy nephritis.

Conclusion

Monoclonal antibodies are emerging with a great hope for refractory and primary renal diseases. This mini review was for glomerulonephritis and detailed discussion of their role in nephrotic syndrome and transplantation is beyond scope of this review. Although future of immune mediated kidney diseases lies with monoclonal antibodies, but cost is limitation till date. Efficacy and safety both have been shown in glomerulonephritis and with more data results; we shall be able to have their superior role in guidelines.

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