BIOLOGIC THERAPY FOR AUTOIMMUNE DISEASES: AN UPDATE

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Abstract

Biologic therapies targeted at cytokines, B cells, and co-stimulation molecules playing a role in the mechanisms of the immune system provide an enhanced method of treatment lacking without many of the serious adverse events encountered with traditional immunosuppressive drugs. We update the literature of the recent years on the new biologics available. We concentrated our efforts on the following drugs: tocilizumab, rituximab, ofatumumab, belimumab, epratuzumab, abatacept, golimumab, certolizumab, sifalimumab as therapies for rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, and vasculitis.

Comment [T2]: Here you could address ref 1’s comment about biologic therapies also having adverse effects
**Introduction**

Biologic therapies for autoimmune and rheumatologic diseases are rapidly expanding due to their good beneficial and safety profiles. This is possible due to better understanding of the initial targets of altered immune regulation and activity in the various diseases.

Targeted therapies are less of a burden for the patient management and are generally have less deleterious adverse events than are encountered with conventional immunosuppression, cyclophosphamide or other conventional immunosuppressive agents. The major targets are anti-cytokines, B cells, and co-stimulation molecules. Anti-cytokines include TNF blockade, anti-IL-1, and anti-IL-6. B cell depletion includes anti-CD20 antibodies and BCR modulation by B lymphocyte stimulator (BLyS). While some of the biologics are found to be useful in more than one disease, others are specific for one disease. Research is ongoing to find other targets. In this review, we will update new agents available for clinical treatment in the past 5 years for rheumatoid arthritis, spondyloarthropathy, systemic sclerosis, systemic lupus erythematosus (SLE), and vasculitis.

**Methods**

We did a thorough literature review in English from 2007 to April 2012 utilizing PUMBED database for the terms rheumatoid arthritis, spondyloarthritis, systemic sclerosis, systemic lupus erythematosus, and vasculitis matched to the terms biologics, tocilizumab, rituximab, ofatumumab, belimumab, epratuzumab, abatacept, golimumab, certolizumab, and sifalimumab. We searched for randomized controlled trials, case series, and excluded case reports. We excluded biologics that are presently investigated yet not available in the clinical setting. We excluded articles that are not in English.

**Screening for biologic treatment**

More than a decade has passed since the beginning of biologic therapy. Screening prior to administration is a routine practice. Screening often is performed at the initial visits to prevent unnecessary waiting when a biologic is indicated. Screening consists of evaluation of prior or present tuberculosis (history, PPD, chest xray), serological evidence of hepatitis B and C, history of malignancies or neurological...
disease. Based on screening, the physician will assess which biologic treatment is recommended or if prior treatment is warranted before the initiation of the biologic therapy.
**Tocilizumab (Actemra, Roactemra)**

**Mechanism:**
Tocilizumab (TCZ) is a recombinant monoclonal IgG1 antihuman interleukin 6-receptor antibody [1]. IL-6 binds to IL6-R either membrane bound or soluble; together they bind to 130gp signal transducer enhancing the inflammatory cascade, inducing angiogenesis and enhancing adhesion molecules and activation of osteoclasts activation [2,3]. IL-6 is also responsible for activating the T helper cells, B helper cells, and B cell differentiation, thus by blocking IL-6 the inflammatory response is decreased [2].

In rheumatoid arthritis (RA) patients, a high level of IL-6 was found in the synovium of involved joints and in the blood. In an animal study, injecting TCZ to the inflamed joints reduced the swelling and the inflammatory response [2,4].

**Indications and dosage:**
TCZ is indicated for the treatment of RA after following an inadequate response or treatment failure with disease modifying anti-rheumatic drugs (DMARD) or with tumor necrosis factor antagonist (anti-TNF) and for systemic juvenile idiopathic arthritis (SJIA). In addition, TCZ is indicated in Castleman's disease.

The recommended dose of TCZ is 8 mg/kg, every 4 weeks. In the United States, it was approved for RA in January 2010, but the recommended starting dose is 4 mg/kg administered once every 4 weeks followed by an increase to 8 mg/kg depending on clinical response [5,6].

Administration is intravenously at a dosage of 4 mg/kg up to 8 mg/kg up to a maximal single infusion dose of 800mg every 4 weeks for RA and 12 mg/kg or 8 mg/kg depending on body weight for SJIA [7]. Simulations within a large rheumatoid arthritis (RA) population showed that disease activity score (DAS) remission rates were 38% for 8 mg/kg and 24% for 4 mg/kg [7].

**Efficacy:**
A meta-analysis examined the double blind, randomized, placebo reviews from the literature including abatacept, rituximab, anti TNF alpha, etanercept, infliximab, and adalimumab compared to TCZ in inadequate responders to DMARDs and anti TNF. TCZ
was non inferior compare to the other biological treatment according to the American College of Rheumatology (ACR) response 20/50, and was superior in the ACR 70 [8]. Furthermore the response to TCZ was early, soon after the first infusion [1]. A monotherapy of TCZ for 52 weeks showed significantly less radiographic change in the total Sharp score compared to DMARDs [2]. In a study of 24 weeks comparing TCZ and methotrexate (MTX), non-inferiority was demonstrated and superiority in the 2nd week in the intention to treat group of the TCZ measured by the ACR20 [3]. Several other studies were conducted comparing monotherapy of MTX to TCZ demonstrating superiority of TCZ [3,9]. In a study of 1196 RA patients that responded partially to MTX treatment showed suppression in radiographic progression and improvement in physical function [9]. Studies demonstrated response to TCZ in RA patients failed to respond to anti TNF [9].

**Adverse effects and safety:**

In the treatment of moderate to severe RA, favorable results regarding the safety of TCZ were demonstrated both in the short term treatment and the as well as long term compared to other treatment modalities [e.g. anti-tumor necrosis factor alpha (TNF)]. In a meta-analysis, TCZ was well tolerated for more than 2.4 years and had less severe adverse effects compared to other biologics [8]. In a study of 286 patients for 24 week treatment, 66.1% of patients experienced adverse events related to the drug, however, those were mild to moderate and transient. The small number of patients experiencing serious adverse events developed infections [1].

In a study integrating the 3 phases of TCZ safety, the adverse events were similar to the other treatment groups (DMARDs, anti-TNF alpha). The most common adverse events were infections, mostly of the upper respiratory tract and gastrointestinal disorders [10]. More severe adverse events were cardiac events, serious infections and malignancies of solid organs, non-melanoma skin tumors, and hematological [10]. It should be stated that higher rates of serious infections were related to previous anti-TNF treatment. The most common infections were pneumonia, gastroenteritis, and urinary tract infections [10].

Several patients were diagnosed with Tuberculosis despite screening prior to treatment according to guidelines. Higher doses of TCZ (8 mg) were associated with higher risks for infections but remained similar to the rate encountered with DMARDs or anti TNF-
alpha [10]. Gastrointestinal perforation occurred in 16 patients exposed to TCZ in the phase 3 trials out of which 11 had diverticuli with a female predominance [10].

In those patients that developed abnormal liver function tests there was a small number of patients with an significant increase in liver function levels ALT above 3 folds and, a dose reduction was sufficient for the continuation of the study [10]. Only 2.3% of exposed patients had to stop the treatment; however no clinical significance was noted in all patients [10].

Neutrophil decline was observed in patients receiving TCZ which stabilized following however, it remained stable after two weeks of therapy. In those patients with grade 4 neutropenia, discontinuation of the therapy lead to an increase in the neutrophilic count [10].

In different studies of monotherapy with TCZ, the most common adverse events were nasopharyngitis, gastrointestinal symptoms and infections. No difference in the incidence of adverse events was demonstrated compared to other treatment modalities [3], TCZ is associated with increased cholesterol levels, an elevated ratio of LDL/HDL, and increased ratio of total to HDL cholesterol (Singh JA) [101].

In conclusion, TCZ is beneficial and safe for RA patients who are non-responders to anti-TNF therapy or when such therapy is contraindicated.

**Rituximab (Rituxan, Mabthera)**

**Mechanism:**

Rituximab is a chimeric-human monoclonal antibody against the CD20 protein found on naive, mature, and memory B cells. It depletes the B cell population via apoptosis, cellular cytotoxicity and complement activation cytotoxicity. In a number of studies measuring markers for immature B cells, memory B cells, and pre-B cell colony-enhancing factor (visfatin) B cell depletion was demonstrated after the treatment with rituximab [44,12]. In addition, rituximab affects the interferon I response genes. In RA
patients responding to rituximab treatment, the gene expression increased while the non-responding patients had limited or no activity [1112].

**Indications and dosage:**

For autoimmune diseases, the only indication approved by the FDA is for active RA that is not responsive to DMARD and anti-TNF agents. Rituximab is beneficial for other off-label indications in patients with autoimmune diseases and Castleman’s disease.

Rituximab treatment proved to have extraordinary results in RA patients. In addition, it is utilized for off-label indications in some other autoimmune diseases and the treatment of Castleman’s disease in Japan.

Pretreatment with acetaminophen and an antihistamine is recommended to prevent an infusion reaction. The most popular protocol for RA is intravenous infusion (I.V.) of 1000 mg/m² on days 1 and 15 in combination with methotrexate; subsequent courses may be administered every 24 weeks (based on clinical evaluation), and if necessary, may be repeated no sooner than every 16 weeks. For patients with RA, premedication with methylprednisolone 100 mg I.V. (or equivalent) is recommended 30 minutes prior to each dose [1113].

In Wegener’s granulomatosis (WG) the protocol is different: I.V. infusion with 375 mg/m² once weekly for 4 doses (in combination with methylprednisolone I.V. for 1-3 days followed by daily prednisone). The protocol for microscopic polyangiitis (MPA) is similar [1114].

Chronic immune thrombocytopenic purpura (ITP): (unlabeled use) In a multicenter phase II study of 60 patients, an I.V. infusion of 375 mg/m² once weekly for 4 doses, 40% of patients achieved a steady platelet level [1415]. A few studies suggest that treatment with 100 mg/m² would suffice with less adverse events or with combination of steroid treatment however data is lacking regarding this dose [1415].

Refractory pemphigus vulgaris: (unlabeled use) The recommended dose is I.V. infusion of 375 mg/m² once weekly of weeks 1, 2, and 3 of a 4-week cycle, repeat for 1 additional cycle, then 1 dose per month for 4 months (total of 10 doses in 6 months) [1516].

Initial infusion: Start rate of 50 mg/hour; if there is no reaction; increase the rate by 50 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour.
Several studies demonstrated that rituximab in the treatment of systemic sclerosis may be beneficial [16,17]. In a study of 8 systemic sclerosis patients following rituximab therapy B cell infiltrate was depleted from the patient's skin, suggesting a possible therapy for skin fibrosis [16,17]. Another study of 15 patients demonstrated histological skin improvement of systemic sclerosis patients following rituximab therapy [16,17].

**Efficacy:**

In a study of 257 SLE patients, a follow up of disease activity was performed under the treatment of rituximab and prednisone. There were no differences between the groups. However, it should be stated that in a subgroup analysis of African American and Hispanic there was a significant benefit to the rituximab group. Furthermore, in open trials for long term treatment superiority of rituximab was noticed [17,18].

The lack of efficacy could be secondary to the clinical set up of the trial, inclusion of too many subsets, or non-stratification of anti-dsDNA positive or negative patients [Tew. Lupus 2010] [18].

In a study of 646 RA patients who had treatment failure with anti TNF blockers, 6 month therapy with rituximab resulted in good clinical response and even remission of the disease [18,19,20].

In the SUNRISE study, 559 RA patients that had inadequate response to one or more TNF inhibitor were given two treatment cycles of rituximab to assess the beneficial and safety profile. Of the total number of patients in the study, 475 patients received the 2nd cycle of therapy and responded significantly compared to the placebo group measured by the ACR20 [21].

In a study of 42 patients with severe pemphigus vulgaris, rituximab was administered as a monotherapy. Remission was induced in 36 patients for 8 to 64 months. In those patients requiring an additional dose, the safety profile remained good [22].

A case series shows that rituximab may help in hemolytic anemia, thrombocytopenia, and arthritis related lupus [23].

**Adverse effects and safety:**

Rituximab treatment requires the monitoring of several side effects namely infections, tuberculosis and lymphoma [20,22]. It is contraindicated in the case of active infections.
live vaccination, a five years history of non-lymphoproliferative cancer, CHF, severe congestive heart failure, NIH A III-IV, a history of demyelinating disease, breastfeeding, and pregnancy and breastfeeding [24,25].

In a meta-analysis of 2578 patients from different studies analyzing the safety of rituximab including long term therapy, 123 patients withdrew due to severe infusion reaction, malignancy, infection or cardiac event [24,25]. Most adverse events occurred during the first course and mostly due to an infusion reaction that can be avoided by slower infusion rate and proper premedication. The incidence of malignancies is no different between RA patients and those treated with rituximab [26,27].

Rituximab causes a decrease in gammaglobulin concentrations, depending on the cumulative doses, however no higher risk for severe infections are noticed [28,29]. It should be stated that a few cases of progressive multifocal leukoencephalopathy (PML) were documented in patients post rituximab therapy, in a study assessing the safety of long term therapy one patient developed PML after 18 month of rituximab therapy in a patient receiving chemotherapy [26,25].

Ofatumumab (Arzerra)

Mechanism:

Ofatumumab is a fully human monoclonal antibody directed against the membrane proximal epitope on CD20 molecule [30,31,32].

Indications and dosage:

Ofatumumab is indicated in the treatment of chronic lymphocytic leukemia. Due to its B cell suppression effect it is also indicated in the as off-label treatment of RA in patients with MTX therapy failure or partial stabilization of the disease in the USA and Europe.

In a study of combined phase I and II, patients received 3 doses in ascending dose of 300 mg, 700 mg, and 1000 mg given I.V. in 2 separate administrations with 2 weeks in-between, over a period of 24 weeks [33,34,35]. Prior to the administration, all patients received acetaminophen, antihistamine, and glucocorticoids in the high dose groups.
The recommended dose according to efficacy and safety concern is 700 mg 2 weeks apart each dose given intravenously over 4 hours with appropriate pre-medication.

Efficacy:

Two studies demonstrated efficacy comparing Ofatumumab to placebo or MTX in a prior treated patients with DMARDs or biologics that were discontinued prior to the study. In one study, comparing 3 doses groups to placebo with MTX treated patients, the efficacy of the ofatumumab groups achieved significantly higher rates of ACR20 compared to the placebo. In addition, the beneficial effect of the high dose group was significantly higher than the low dose group assessed by the ACR20 and circulating B cells population.

In another study of multi-centered double blind randomized control study of biologics naïve patients comparing ofatumumab at a dose of 700 mg treated patients to placebo, a higher rate of improvement measured by ACR20 was noted in the ofatumumab group significantly. It should be stated that no statistically significant differences were noticed between seronegative and seropositive RA patients in the results.

Adverse effects and safety:

In a study comparing the safety of ofatumumab in 3 different doses the main adverse events were related to infusion reaction that was mild to moderate and mainly at the first and second administration which decreased after pre-medications. After 24 weeks of treatment, a significant number of adverse events were noticed in the 1000 mg dose group. It should be noticed that no difference in infections were noticed between the 3 groups and the placebo. Further adverse effects were: rash, dyspnea, rhinitis, nausea, pruritus, upper respiratory tract infections, headaches, fatigue, flushing, hypertension, exacerbation of RA, and diarrhea.

In another double-blind multicenter study, the same adverse reactions were noticed with the most common reaction being urticaria and rash on the day of the first infusion. Most of the reactions were mild to moderate except for 6 patients with 7 severe adverse effects that accounted for 5% (1 fatal). No cases of progressive multifocal leukoencephalopathy were reported.
Belimumab (Benlysta)

Mechanism:
The BLyS protein is a member of the superfamily of tumor necrosis factors that inhibits B-cell apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells. Belimumab is a human monoclonal immunoglobulin IgG1 gamma, which binds to the soluble form of BLyS protein hence leading to its inhibition [25267,26228].

Indications and dosage:
Belimumab is FDA approved for the indicated treatment of mild- moderate SLE therapy, excluding active lupus nephritis or neuropsychiatric involvement [25267,26228]. It is given IV slowly over 1 hour at a recommended dose of 10mg/kg at two week intervals for 3 infusions, then every 4 weeks [25267,26228].

Efficacy:
In a phase II trial, there was only a significant effect of belimumab after 52 weeks of therapy in its steroid sparing effect and not in disease activity scores in patients with severe active disease [25267]. However, in the phase III clinical trials it was demonstrated by the SLE Responder Index (SRI) (an index that incorporates disease activity scores to compile a single score) had significant improvement in both the 1 mg/kg group and the 10 mg/kg group compared to the placebo [26228]. Furthermore, significant changes were noticed in Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), and non-inferior compared to the placebo in the Physician’s Global Assessment [PGA] score [26].

Adverse effects and safety:
The most common adverse reactions with belimumab treatment are nausea, diarrhea, headaches, and upper respiratory tract infections. Less common side effects are fever, cystitis, leucopenia, infusion reaction, and severe infections. Studies demonstrated that the number of adverse events in belimumab group compared to the placebo group were similar. Furthermore, the severity and number of adverse events did not increase when high dose therapy was utilized (1 mg/kg compared to 10 mg/kg) [25267,26228].
**Epratuzumab**

**Mechanism:**
Epratuzumab is an IgG1 monoclonal antibody directed against CD 22 molecule. CD22 is a B-cell-specific transmembrane sialoglycoprotein inhibiting the B cell receptor complex causing early apoptosis thus shortening the cells life span [27][28][29].

**Indications and dosage:**
The therapeutic dose is 360 mg/m² every 2 weeks up to 4 times, given IV over one hour. It is recommended that prior to infusion acetaminophen and anti-histamine should be given to the patients to minimize infusion reaction [28][29][30]. Due to its anti CD 22 targeting, epratuzumab is indicated in the treatment of SLE and Sjögren's syndrome [28][29][30].

**Efficacy:**
Although epratuzumab has not received regulatory approval for SLE and Sjögren's syndrome, several studies were conducted treating patients with epratuzumab (excluding patients that were treated with rituximab). In a study measuring the British Isles Lupus Assessment Group (BILAG) score in a follow up of 6 months, all patients had a decrease in more than 50% of disease activity [28][29][30]. In a larger study of 227 patients with moderate to severe SLE receiving doses of 600 mg, 800 mg, 2400 mg, and 3600 mg for 12 weeks, compared to placebo, all responded to therapy significantly, demonstrated by BILAG score [28][30]. In a different study of Sjögren's syndrome patients, 67% of patients responded to therapy after 6 month demonstrating indicative of the regeneration of glandular tissue [28][30].

**Adverse effects and safety:**
In the phase II trial of 227 patients, there was no significant difference between all the study groups receiving epratuzumab compared to the placebo group [28][30]. In SLE patients most of the adverse events were minor such as nausea, fatigue, general pain, and infusion reaction that can be avoided by administrating acetaminophen and/or antihistamine prior to therapy [28][30]. In Sjögren’s syndrome patients, more severe
adverse effects were noted during the infusion due to nasal mucosa swelling and glottis pressure [28-30].

Abatacept (Orencia)

Mechanism:
T cells play a major role in the pathogenesis of rheumatoid arthritis (RA). By co-activation T cells’ CD28 with the antigen presenting cells (APC) protein CD80/86, inflammatory cytokines are released. CTLA-4 is a protein with a high affinity to CD80/86 inhibiting the T cell activation (by blocking the CD28 binding). Abatacept is a CTLA-4 IgG1 binding to the CD86/80 on APCs inhibiting the co-stimulation of CD28 on the T cells [303-32].

Indications and dosage:
Abatacept is FDA approved indicated for the treatment of rheumatoid arthritis non-responsive to DMARDS and anti-TNF drugs and Juvenile idiopathic arthritis (JIA).
In RA treatment, the dose is given according to body weight ~ 10mg/kg: <60 kg: 500 mg, 60-100 kg: 750 mg, >100 kg: 1000 mg. Initial dose is given intravenously, following with additional I.V. dose after 2 weeks and 4 weeks afterwards repeating every 4 weeks.
Another option is, following the initial I.V dose, within 24 hours injecting subcutaneously a dose of 125 mg and then continuous subcutaneous weekly injections [303-32].
In the treatment of JIA the treatment is given I.V. as well, the dose is according to body weight and age: Children ≥6 years and <75 kg: 10 mg/kg, 75-100 kg: 750 mg, >100 kg: 1000 mg.
In a multi-centered double blind placebo controlled study of 180 lupus patients with discoid rash, serositis, or polyarthritis manifestations Patients-patients received the same dosage as in RA patients-[34-33].

Efficacy:
In a meta-analysis of both phases II and III, including an extension phase, improvement in disease activity in RA patients, measured by the ACR score, was noticed with combined abatacept and DMARDs within 6 months and in patients that didn’t respond to anti-TNF therapy. For the ACR20, an average of 50% improvement was noticed compared to 30% in the placebo group. Comparing to placebo groups and other treatment modalities, similar results were noticed in the ACR50 and ACR70. In a long term study comparing the treatment of abatacept and placebo (with a background therapy of steady dose of methotrexate), the response to abatacept was superior and maintained for 3 years. Similar results were noticed in physical function scales. The evaluation of radiographic changes demonstrated a reduction in Genant-modified Sharp scores, bone erosion score, every year within the 3 year follow up and 40% of patients had no radiographic progression after 3 years.

In the study of the 180 lupus patient’s abatacept had a steroid sparing effect, demonstrated with a lower number of flare-ups in the abatacept receiving patients with concomitant low dose steroid treatment. This effect was seen mostly in the polyarthritis presenting lupus patients. Furthermore in the abatacept group significant improvement was noted in the patients reported score as well.

**Adverse effects and safety:**

The main adverse events that are caused by abatacept include infections, upper respiratory tract symptoms, nausea, headache, infusion reaction, fever, hypertension, back pain and limb pain.

In a study of long term safety, 96% of patients experienced adverse effects however most of them were mild to moderate and mostly related to infections. No unexpected safety events were observed in the LTE. Some deaths were noted from cardiovascular events, malignancy and serious infections. Furthermore in studies of RA patients with refractory disease to anti TNF alpha treatment a significant improvement of 50% in the ACR20 score was noted after one month of treatment and even further after 6 months of therapy. The physical function score improved as well. No significant differences in the adverse effects were noted comparing abatacept and the placebo group (receiving DMARDs only).
**New Novel anti-TNF-alpha blockers**

**Golimumab (Simponi)**

**Mechanism:**
Golimumab is an IgG1 fully human monoclonal antibody, acting on TNF alpha both
soluble and membrane bound [35367].

**Indications and dosage:**
The treatment is FDA approved for indicated in RA, psoriatic arthritis, and ankylosing
spondylitis (AS) [35367, 383940].

It is given via subcutaneous injection. The indicated dose for all indications is 50 mg
once in a month via subcutaneous injection. In RA patients, it is indicated in combination
with methotrexate [37389].

In a study comparing treatment groups of 50 mg and 100 mg doses, no significant
difference was noted between the two groups. The lower dosage is the recommended one
clinically [35367].

**Efficacy:**
In a study of AS patients comparing patients receiving golimumab at different dosages
for 24 weeks, a significant improvement was seen in the AS International Working Group
criteria (ASAS20) in the golimumab groups compared to the placebo group
[35367, 383940]. A similar study was performed in psoriatic arthritis patients comparing
2 groups of golimumab at different dosages, resulting in a significant improvement in the
golimumab groups measured by the ACR20 score, physical function scores and nail and
skin disease involvement [36378, 383940]. Furthermore significant improvement in
enthesitis and in the dactylitis severity score (in patients receiving 100mg) was noted
[36378]. A total of 6 randomized control trials reported significant improvement for
dactylitis and enthesitis in psoriatic arthritis patients [39401]. In a study of RA patients,
comparing the efficacy of patients receiving MTX with placebo, with golimumab or
golimumab with placebo the most significant results were seen in the methotrexate group
with golimumab at 50 mg and 100 mg doses even compared to the methotrexate alone.

However, in the 100 mg group, a higher incidence of adverse events was noted.

Comment [T14]: Please discuss why golimumab did not achieve its primary
outcome in one of the trials (ref 3)
In a study (GO-BEFORE), comparing the treatment of MTX, golimumab at different dosages and placebo in RA anti TNF and anti MTX naïve patients, significant response was shown in the disease activity score (DAS28), ACR70, ACR90, and health assessment questionnaire (HAQ) \([38,39,40]\). It should be stated that in this study the primary outcome of ACR50 was not achieved \([38,39,40]\). Another study (GO-FORWARD) in RA patients, comparing the same groups of anti-TNF naïve patients that were treated with MTX and still had active disease (poor response to MTX), showed improvement in the ACR20 and HAQ reaching the primary end points \([38,39,40]\). A third study (GO-AFTER) of RA patients, comparing patients that were exposed to anti-TNF were treated with golimumab compared to placebo. Significant results were reached in the ACR20 end point \([38,39,40]\).

It should be stated that better results were seen in the groups of the studies above receiving combined therapy of golimumab and DMARD's \([38,39,40]\).

**Adverse effects and safety:**

The main adverse effects are infections, mostly upper respiratory tract and nausea. Additional adverse effects are: hypertension, and increase in liver enzymes (patients with latent Tb were required to take prophylactic treatment for Tb resulting in higher elevations in liver enzymes), paresthesia, dizziness, constipation, local skin reaction and malignancy (basal cell carcinoma, squamous cell carcinoma, prostate cancer, lung cancer, breast cancer) \([35,36,37,38,39,40]\).

In studies made performed assessing regarding golimumab safety, more infections were noted in patients receiving golimumab compared to the placebo \([34,35,36,37,38,39]\). In psoriatic arthritis patients, in the high dose group of patients that received 100 mg had significantly higher rates of infections were noted compared to the 50 mg dose, but were mainly minor infections involving the upper respiratory tract \([36,37,38,28]\).

**Certolizumab pegol (Cimzia)**

**Mechanism:**
Certolizumab is a pegylated humanized antibody Fab fragment of TNF alpha monoclonal antibody binding and inhibits TNF alpha. The pegylation extends the substance half life time while the missing Fc fragment nullifies the risk for cytotoxicity [40412].

**Indications and dosage:**
It is FDA approved indicated for the treatment of active RA disease, given subcutaneously 400 mg every 2 weeks for 3 consecutive treatments followed by maintenance therapy of 200 mg every 2 weeks.

**Efficacy:** In a study of RA patients, patients having the diagnosis for at least 6 month and no more than 15 years were enrolled. The enrolled patients didn’t received biologics therapy 6 month prior to the study and if they were treated in the past with anti-TNF responded to it. 2 groups were compared, patients treatment with methotrexate and placebo compare to cetolizumab and MTX. The ACR20 response and physical improvement backed with less radiographic progression in the combination groups was achieved more rapidly in the cetolizumab group showing over a year [9,40412]. In a different study of RA patients that experienced treatment failure with DMARDs, a significant response ACR20 of up to 50% was encountered. Similar results were noticed in disease activity, physical function, and arthritic pain [41423].

**Adverse effects and safety:**
Other than the adverse reaction recognized for the treatment of TNF alpha blockers, higher incidences of serious infections were noted from cetolizumab [40412]. It should be noted the higher incidence of adverse events occurred at the low dose of 200 mg treatment group but not the higher dose of 400 mg [40412]. In a study of RA comparing cetolizumab to placebo, in a safety studyin RA patients, the adverse events of cetolizumab were headache, nasopharyngitis, diarrhea and sinusitis [44423]. A significantly higher incidence of serious adverse events was noted in patients receiving cetolizumab. These were and included bacterial arthritis, salmonella arthritis, increased blood creatinine/increased blood urea, ischaemic stroke, menorrhagia and mastitis [44423]. No fatalities were reported and no cases of drug induced systemic lupus were reported [44423].
Sifalimumab

Type I interferon plays a part in the SLE pathogenesis. Overexpression of BAFF mRNA was observed in whole blood from some SLE patients as compared with normal controls. The effect of anti-IFNα Ab was examined on B lymphocyte stimulator/BAFF showing suppression of BAFF mRNA via PCR [42, 44]. Sifalimumab is an anti-IFNα monoclonal antibody (mAb) that was evaluated in phase I trial in SLE patients. In the trial no drug related adverse events were noted and no increase in viral infections was observed. In the trial, improvement in disease activity compared to the placebo group was noted [43, 45]. In a phase I study multicenter double blind trial prior to administration and on several occasions of the study anti-sifalimumab antibodies were not detected in all 33 sifalimumab receiving patients [43, 45]. Sifalimumab is currently in phase III trails [49, 51].

IL-1 inhibitors for Gout

The treatment with IL-1 inhibitors are investigate for the therapy of acute gout flare ups. Several drugs are being investigated (Anakinra, Canakinumab, rilonacept, however for now there are no approved indications for treatment of gout due to the adverse effects. risk compare to the efficacy.

Except for, Anakinra (Kineret), which is FDA approved for RA, other interleukin-1 blockers are available. Canakinumab (Ilaris) is specifically indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). It is administered for adults at a dosage of 150 mg subcutaneously every 8 weeks.

Riloncept (Arcalyst) is an interleukin-1 blocker specifically indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 12 years of age and older including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).
age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). It is administered for adults at a dosage of 320 mg subcutaneously on day one and then 160 mg once weekly.

The treatment with IL-1 inhibitors are investigate for the therapy of acute gout flare ups. Several drugs are being investigated (Anakinra, Canakinumab, rilonacept). As of the writing of this article, there are no approved indications for treatment of gout due to the safety risks compare to the efficacy [46,47].

In a Cochrane meta-analysis of adverse events following treatment with biologics in RA patients, it was concluded that treatment with biologics may cause severe infections, reactivation of tuberculosis, or the development of opportunistic infections [44,45,11]. Certolizumab is the only biologic drugs that lead to statistically significant more severe adverse events. However, infliximab was the drug that had statistically significant more total adverse events (of all severities) compare to placebo [44,45,11]. It should be stated that "old" anti TNF drugs had higher incidence of psoriatic arthritis.

IMMUNOGENICITY OF THE NEW BIOLOGICS
**Intravenous immunoglobulin therapy**

**Mechanisms:**
IVIG utilization is well established for immunodeficiency diseases and is beneficial for autoimmune diseases [4546]. The immunoglobulins (Ig) are derived from a pool of thousands of healthy donors, containing antibodies to self and foreign antigens. Several mechanisms are known and influence the immune system at many levels. IVIG has a direct neutralization effect on pathogenic antibodies, B cells, T cells, and macrophage regulation. It inhibits the differentiation and maturation of dendritic cells and prevents the presentation of self-antigens, modulates interleukin 1 receptor antagonist and inhibits BlySS activity [4647].

**IVIG dosage protocols**
The characteristics of the various IVIG products are found on the internet and will not be discussed here (http://www.medprorx.com/forms/MeProRx_IVIg_chart.pdf). Different IVIG protocols are employed depending on the indication for utilization. In systemic autoimmune diseases such as SLE, a high dose protocol is generally considered and consists of 2gr/kg divided over 5 days. This is repeated every 4 weeks, a time period in which the immunoglobulin level in the serum returns to normal. The course is repeated every month, usually up to 6 months, and then every 2-3 months if required. Long term therapy remains beneficial [4748]. A single dose of hydrocortisone 100-200 mg can be administered on day 1 prior to the initiation of IVIG therapy to reduce the side effects. Treatment with low molecular weight heparin in a single dose prior to IVIG initiation is suggested to prevent possible thromboembolic adverse events [4849]. Low dose therapy (400 mg/kg over 1 day every 3-4 weeks) is beneficial for organ-specific disease predominantly in neurological diseases [4748]. It may be beneficial for some cases of mild to moderate lupus [4950].

**Beneficial effects**
IVIG plays a role as an adjunct therapy for SLE patients who are refractory to conventional therapies. This therapy may also be an option for young women who refuse
the conventional immunosuppressive therapies because of disfiguration or sterility as part of the many side effects of these medications. Among the various case reports and case series, high dose IVIG is beneficial for moderate to severe SLE. It has been utilized for serositis, cardiopulmonary disease, hematological manifestations, diffuse neuropsychiatric disease, and lupus nephritis [505, 525, 535]. IVIG was an adjunct therapy to patients with refractory disease or patients that refused cytotoxic drugs. In SLE patients, IVIG had a steroid sparing effect [535, 46]. High-dose IVIG was beneficial for SLE and lead to a decrease in different disease activity scores. IVIG may be useful for recalcitrant cases of organ-specific cutaneous lupus including discoid lupus, subacute cutaneous lupus erythematosus. In many cases, patients received short-term moderate and non high-dose therapy [45, 46]. Serological improvement was also described with a decrease in antibody titer levels and an increase in complement levels [46, 47]. IVIG is utilized for other off-label indications in autoimmune diseases including Sjogren's syndrome polyneuropathy, severe pemphigus vulgaris Still's disease, and relapsing ANCA associated vasculitis [46, 47]. Low dose IVIG is beneficial for Guillain Barre syndrome, Lambert-Eaton syndrome, refractory myasthenia gravis, refractory multiple sclerosis, multifocal motor neuropathy, chronic inflammatory demyelination polyneuropathy, dermatomyositis, and Stiff Man Syndrome [46, 47]. In addition, polyneuropathy in SLE and vasculitis respond well to IVIG therapy [54, 55]. Other diseases in which IVIG is used include ocular involvement in Behcet's disease, Grave's disease, and refractory uveitis, stiff man syndrome, antibody mediated solid organ transplant.

**Adverse effects and safety:**

IVIG is usually associated with mild and transient adverse reactions. The common mild adverse reaction include arthralgia, myalgia, weakness, abdominal pain, diarrhea, blood pressure changes, pulse changes, chills, dizziness, drowsiness, fatigue, fever, headache [11]. The more severe adverse reaction are anaphylactic reaction, thromboembolic events, neutropenia, pancytopenia, autoimmune hemolytic anemia, renal failure with acute tubular necrosis, asthma exacerbation, hepatic dysfunction, seizures, acute respiratory distress syndrome, and aseptic meningitis [55, 68]. Adverse events appearing
with the first course may return with further courses [47, 48]. Side effects do not usually worsen with long-term IVIG therapy [47, 48]. Special consideration should be given to patients with prothrombotic risk and to those with renal failure or risk of renal tubular injury (dehydration, renal disease, diabetes). In the case of high risk of thromboembolic event, low molecular weight heparin can be given prior to the initiation of the IVIG course [46, 47]. IVIG is contraindicated in patients with IGA deficiency.
Conclusions

We have reviewed the literature for new biologics available over the recent years and how they are utilized in various autoimmune diseases. Some are new drugs in known classes (TNF blockers and B cell modulators), some are of a new class (BLyS inhibitor).

The adverse events are similar for the biologics, the severe ones including serious infections. Tuberculosis is virtually eradicated due to the recommendations of screening patients prior to the initiation of biologics.

It is advantageous to have a range of effective biologic drugs available for patients with severe or resistant disease. Severe disease can include involvement of vital systems, steroid resistant disease, persistent disease despite conventional therapy, or even persistent and non-responsive disease despite certain biologic therapies. Different drugs from the same class (for example anti-TNF blockers) may provide a further therapeutic effect. If a patient has an adverse effect from one anti-TNF, he can switch to another TNF blocker or to another class of drugs for example B cell modulators. Or, if there was an initial beneficial response which ceased over time, one can switch to another biologic class drug. With the various available biologics, the physician can customize the therapy to the specific individual. For example, the physician may choose IV therapy for the patient that needs medical supervision or subcutaneous therapy for the patient that feels confident to take the drug in the privacy of his home. The choice of biologic may be customized to include considerations of co-morbidities or the need for concomitant drugs. There is a focus on early treatment, yet none of the biologics are yet available as first-line medications for autoimmune diseases probably due to economic concerns. Since the complexity of preparing the biologics has diminished over the years, hopefully we will consider in the near future administering the biologics at an early stage of disease and hence enable prevention of irreversible damage.

CONCLUSIONS

Please make a statement about the approved biologics and the non-approved as of yet. Are there any new indications or side effects? Have any new biologics added efficacy or safety issues that were not found in anti-TNF patients. Try to mention which patients would be the targets for the new biologics. The new biologics therapy is giving...
additional treatment options for those patients that didn’t respond to the traditional therapy with mainly mild to moderate adverse effects of respiratory infections, prodrominal symptoms and gastrointestinal complaints, with decreased risk for severe complications (e.g. PML). Despite the fact that some of the new drugs still hold higher risk for increased adverse effects it is "the price" to pay for more therapeutic option for those patients resistant to the traditional therapy that was available up to today.

The arsenal of biologics available for the treatment of autoimmune diseases is quickly expanding as a result of better understanding of molecular mechanisms together with improved capacity of production. They include by classes: novel anti-TNF agents (fully humanized or pegylated), anti-interleukin agents (to IL-1, IL-6), B cell directed therapies (to CD20, CD22, interferon la), coactivation signaling (CTLA4-Ig), and immunoglobulins (IVIG). While most of the FDA approved biologics are for RA, Benlysta is the first FDA approved SLE targeted therapy. In addition, the beneficial and safety for off-label indications of biologics are encouraging for resistant autoimmune patients.

**Competing interests:** The authors do not have any competing interests.

**Authors’ contribution:** Dr. Rosman and Dr. Zandman-Goddard contributed equally to the literature search, review of the pertinent articles, and writing of the article. Prof. Shoenfeld contributed to the concept, editing and critical appraisal of the article.

Comment [T17]: Please provide the following sections at the end of your manuscript 1. Competing interests 2. Authors’ contributions 3. Authors’ information 4. Acknowledgements More information about what to include in these sections can be found at http://www.biomedcentral.com/bmcmed/authors/instructions/review#formatting, competing I think your review would also benefit from a list of abbreviations here, as quite a lot are used in the text.
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   2011, 17:3166-75.  
   Long-term therapy with intravenous immunoglobulin is beneficial in patients  


## Update on biologic therapy in autoimmune diseases

<table>
<thead>
<tr>
<th>Drug (pharmaceutical name)</th>
<th>Mechanism</th>
<th>Indications</th>
</tr>
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<tbody>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>recombinant monoclonal IgG1 antihuman interleukin 6-receptor antibody [1]</td>
<td>RA after treatment failure with anti-TNF, SJIA [5,6]</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra)</td>
<td>fully human monoclonal antibody directed against membrane proximal epitope on CD20 molecule [2325]</td>
<td>RA, chronic lymphocytic leukemia [2325-2426]</td>
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<tr>
<td>Belimumab (BenlystaBenlysta)</td>
<td>human monoclonal immunoglobulin IgG1 gamma, that binds to soluble form of BLyS protein inhibiting it [2527,2628]</td>
<td>SLE except lupus nephritis or central nervous system lupus [2527,2628]</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>IgG1 monoclonal antibody directed against CD 22 molecule [2729,2830]</td>
<td>SLE, Sjögren’s syndrome [2830,2931]</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>CTLA-4 IgG1 binding to the CD86/80 on antigen presenting cells inhibiting the co-stimulation of CD28 on the T cells [4032]</td>
<td>RA, JIA, lupus-SLE – discoid, serositis and arthritis manifestations [4032-4433]</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>IgG1 monoclonal antibody, acting on TNF alpha both soluble and membrane bound [4337]</td>
<td>RA, psoriatic arthritis, ankylosing spondylitis [3537-4840]</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
<td>pegylated humanized antibody Fab’ fragment of TNF alpha monoclonal antibody [4042]</td>
<td>RA [4042]</td>
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<tr>
<td>Sifalimumab</td>
<td>an anti-IFNα monoclonal antibody [4244]</td>
<td>Phase I trial – not in use yet</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>Pool of immunoglobulins from healthy</td>
<td>SLE, systemic sclerosis,</td>
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Table: Treatment Options for Periodic Syndromes and Vasculitis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Anakinra</td>
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<td>RA</td>
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<tr>
<td>Ilaris</td>
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<td>Cryopyrin-Associated Periodic Syndromes [46–47]</td>
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<tr>
<td>Arcalyst</td>
<td>Interleukin-1 blockers</td>
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</tbody>
</table>
*FDA approved indication*

**Abbreviations:**

- Tocilizumab (TCZ)
- Rheumatoid arthritis (RA)
- Tumor necrosis factor antagonist (anti-TNF)
- Juvenile idiopathic arthritis (JIA)
- Half maximal effective concentration (EC50)
- American College of Rheumatology (ACR)
- Methotrexate (MTX)
- Disease modifying anti rheumatic drugs (DMARD)
- Wegener’s granulomatosis (WG)
- Microscopic polyangiitis (MPA)
- Immune thrombocytopenic purpura (ITP)
- Safety of Estrogens in Lupus
- Erythematous National Assessment–Systemic Lupus Erythematous Disease Activity Index (SELENA-SLEDAI)
- British Isles Lupus Assessment Group (BILAG)
- Ankylosing spondylitis (AS)
- Assessment in ankylosing spondylitis (ASAS)
- B lymphocyte stimulator (BLySS)
- Intravenous immunoglobulin (IVIG)
- Health Assessment Questionnaire (HAQ)
- Disease Activity Score (DAS28)
Additional files provided with this submission:

Additional file 1: Biologics for autoimmune disease BMC notes.docx, 100K
http://www.biomedcentral.com/imedia/9302326447744780/supp1.docx