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Immune-Modulating Therapy for Rheumatologic Disease: Implications for Patients with Diabetes

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Abstract

Immune modulators used to treat rheumatologic disease have diverse endocrine effects in patients with diabetes. Providers should be aware of these effects given that diabetes and rheumatologic disease overlap in prevalence and cardiovascular morbidity. In patients with type 1 diabetes, clinical trials have demonstrated that immune modulators used early in the disease can improve pancreatic function, though their efficacy in adults with longstanding autoimmune diabetes is unknown. In patients with type 2 diabetes, hydroxychloroquine is an effective antihyperglycemic and may be preferred for rheumatologic use in patients with difficult glycemic control. In patients without diabetes, hydroxychloroquine and tumor necrosis factor (TNF) inhibitors have been found to decrease diabetes incidence in observational studies. Additionally, dapsone and sulfasalazine alter erythrocyte survival resulting in inaccurate HbA1c values. These multifaceted effects of immune modulators create a need for coordinated care between providers treating patients with diabetes to individualize medication selection and prevent hypoglycemic events. More research is needed to determine the long-term outcomes of immune modulators in patients with diabetes.

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Compliance with Ethical Standards

Conflict of Interest Scott J. Pilla, Amy Q. Quan, Emily L. Germain-Lee, David B. Hellmann, and Nestoras N. Mathioudakis have no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Keywords

Immunomodulation; Immunosuppressive agents; Antirheumatic agents; Diabetes mellitus; Hypoglycemia; Rheumatic diseases

Introduction

Medications that alter the function of the immune system are the foundation of therapy for many rheumatologic diseases [1]. The same immune modulators have a variety of effects specific to patients with diabetes mellitus. These diabetes-specific effects have implications for treatment selection in patients with rheumatologic disease, for the prevention of hypoglycemia, and for adjusting glycemic monitoring for altered erythrocyte survival.

Since rheumatologic disease and diabetes often go hand-in-hand, it is important for clinicians to understand the effects of immune modulators on both conditions. Patients with type 1 diabetes have a greatly elevated risk of developing rheumatoid arthritis (RA) [2, 3], and patients with rheumatologic disease have excess rates of type 2 diabetes, cardiovascular risk factors, and cardiovascular mortality [4, 5]. Given their ability to affect both conditions, immune modulators deserve special consideration in this high-risk population.

We present a review of the literature on the effects of immune modulators for rheumatologic disease among patients with diabetes. We report on the effects of these medications on autoimmune diabetes, including type 1 diabetes and latent autoimmune diabetes of adulthood (LADA), and type 2 diabetes and its prevention. We also discuss the implications of these findings for clinicians.

Fluidity in Type 1 Diabetes Disease Activity

While glycemic control in type 2 diabetes tends to worsen predictably in the presence of certain factors such as weight gain or corticosteroid use, the course of autoimmune diabetes is more fluid and unpredictable [6]. A noteworthy example of this fluidity is the honeymoon phase of type 1 diabetes: a period of decreased insulin requirements that occurs after initiating insulin therapy [6, 7]. It is experienced by approximately half of patients with type 1 diabetes; the onset is usually within weeks of starting insulin therapy but may occur months later, with insulin needs typically returning to baseline after several months [6, 7]. Definitions of the honeymoon phase vary, including combinations of relative insulin dose and glycemic control [8]. Most of our knowledge about the honeymoon phase is derived from studies of children, but it occurs in adults with type 1 diabetes as well [9].

Many immune-modulating medications used to treat rheumatologic disease have been given to patients with type 1 diabetes in an attempt to induce and extend the honeymoon phase. Beginning with cyclosporine in 1984, immune modulators were investigated as potential treatments for recent onset type 1 diabetes in clinical trials [10, 11]. Subsequent trials targeted many components of the immune system including T and B lymphocytes and cytokine pathways [10]. In these studies, the primary outcome was typically a direct measure of pancreatic endocrine function: fasting C-peptide (FCP) or stimulated C-peptide

(SCP), which is more sensitive than FCP but also time-consuming [12]. Secondary outcomes included change in HbA1c and insulin dose and some definition of the honeymoon phase (also referred to as “diabetes remission”). Overall, the utility of immune modulators in recent-onset type 1 diabetes has been limited by drug toxicity and a lack of lasting effects on the natural history of the disease when therapy is discontinued [11]. That paradigm may be changing as less toxic drugs are proving effective, such as seen in a recent clinical trial of alefacept [13•]. Future work is needed to understand the potential impact of newer immune modulators used in rheumatologic disease on type 1 diabetes of recent onset.

Diabetes-Specific Effects of Rheumatologic Immune Modulators

Study Selection

We performed a literature review to identify the effects on diabetes of immune-modulating medications for rheumatologic disease. We searched PubMed from inception to March 2016 using MESH topics: (*immunosuppressive agents* OR *immunomodulation* OR *antirheumatic agents*) AND (*diabetes mellitus* OR *hyperglycemia* OR *hypoglycemia*). We also searched commonly used rheumatologic drugs as [*drug name*] AND (*diabetes mellitus* OR *hyperglycemia* OR *hypoglycemia*). The resultant studies were reviewed and included if relevant to glycemic control, pancreatic function, and/or clinical diabetes management. The bibliographies of identified studies were reviewed for additional relevant publications. Studies were excluded if they were not in vivo studies of humans, not English language, or had pathophysiologic (e.g., insulin resistance by euglycemic clamp) rather than clinical outcomes.

Evidence from randomized controlled trials (RCTs) and large cohort studies is presented in Table 1.

Azathioprine

Azathioprine is a purine analog that interferes with nucleic acid metabolism [14]. It is used as a second-line treatment for RA and off-label (U.S. Food and Drug Administration labeling) for other rheumatologic diseases [1]. Azathioprine was studied in two early trials of patients with recent onset type 1 diabetes. The first of these trials randomized subjects without masking to azathioprine and prednisone versus no treatment and found lower insulin needs and higher SCP in the treatment group at 1 year of follow-up, but no difference in HbA1c [15]. The second trial was a double-blinded RCT of azathioprine alone versus placebo which found no effect on FCP, SCP, HbA1c, nor insulin dose at 1 year [16]. Two small trials using alternating (non-randomized) assignment without placebo found mixed effects [17, 18].

Colchicine

Colchicine is a naturally occurring alkaloid that disrupts microtubule assembly, inhibiting neutrophil function and cytokine activation [19]. It is used for gout prophylaxis and treatment [1]. In a small placebo-controlled crossover study of colchicine in twelve patients with type 2 diabetes, subjects had a significantly lower glucose by oral glucose tolerance test while on colchicine [20]. In patients without diabetes, a large retrospective cohort study

found that colchicine users (matched to non-users by propensity scoring) did not have a significantly lower diabetes incidence (adjusted hazard ratio 0.88; 95 % CI 0.66, 1.16) [21].

Cyclosporine

Cyclosporine is a fungal metabolite that inhibits calcineurin which is an enzymatic component of lymphocyte intracellular signaling [22]. It is used for refractory RA and off-label for several rheumatologic diseases [1]. There have been five RCTs of cyclosporine in recent onset type 1 diabetes [23–27]. In the studies that administered cyclosporine consistently for more than 6 months and evaluated effects on pancreatic function [23, 24], cyclosporine increased SCP relative to placebo, and had no effects on HbA1c and insulin dose. In these studies, effects of cyclosporine on SCP became apparent by 3 to 6 months, and withdrawal of cyclosporine at 1 year resulted in an immediate increase in insulin needs in some subjects [28]. There have been several non-randomized studies of cyclosporine in type 1 diabetes which were consistent with beneficial effects on pancreatic function [29–31].

Cyclophosphamide

Cyclophosphamide is a synthetic DNA alkylating agent that is used off-label for vasculitides and severe systemic complications of rheumatologic disease [1, 32]. There is little evidence of effects of cyclophosphamide on diabetes. There is one case report of cyclophosphamide causing transient hyperglycemia [33], though no other reports were found.

Dapsone

Dapsone is a synthetic sulfone antimicrobial that inhibits bacterial folic acid synthesis and exerts immune-modulating effects in humans by unclear mechanisms [34]. It is used off-label for complications of lupus, some vasculitides, and Beh et disease [1]. Dapsone has no known effects on glycemic control in patients with diabetes; however, it may cause changes in erythrocytes that can falsely lower HbA1c measurements. Dapsone frequently causes hemolysis and reduced erythrocyte survival, even in patients without glucose-6-phosphate dehydrogenase deficiency [35–37]. Dapsone can also cause varying degrees of methemoglobinemia [35, 37, 38]. Each of these effects can interfere with HbA1c measurement resulting in falsely low values [39, 40]. There are numerous case reports of patients with diabetes developing spuriously low HbA1c values on dapsone therapy [41–44].

Glucocorticoids

Glucocorticoids are corticosteroid hormones which are widely used for their anti-inflammatory and immunosuppressive properties [45]. The predominant effect of glucocorticoids on patients with diabetes is to induce hyperglycemia, particularly in the post-prandial period [46]. In addition, glucocorticoids can independently cause new-onset diabetes in non-diabetic patients [47•]. Given its immunosuppressive effects, prednisone was studied as a treatment for new-onset type 1 diabetes in two RCTs. In these trials, prednisone alone increased insulin needs and had no effect on FCP or HbA1c [48], but prednisone in combination with azathioprine increased SCP and reduced insulin needs [15].

Hydroxychloroquine

Hydroxychloroquine is an antimalarial that alters epitope binding of major histocompatibility complex molecules in antigen-presenting cells [49]. It is a first-line treatment for RA and systemic lupus erythematosus and is commonly used off-label for a variety of rheumatologic conditions [1]. It has long been recognized that quinoline antimalarials may have hypoglycemic effects, hypothesized to be due to changes in intracellular insulin metabolism in peripheral tissues [50]. There are case reports documenting hypoglycemia in hydroxychloroquine-treated patients with no prior diabetes [51, 52] and with type 2 diabetes [53–55].

Hydroxychloroquine has been found to be an effective antihyperglycemic in patients with type 2 diabetes. An RCT of adults with poorly controlled type 2 diabetes found that the addition of hydroxychloroquine to standard sulfonylurea treatment reduced HbA1c by 1.02% (95 % CI 0.24%, 1.81%) more than placebo at 18 months of follow-up [56]. In patients with type 2 diabetes on insulin therapy, hydroxychloroquine was also found to significantly reduce HbA1c compared to placebo at 6 months of follow-up [57]. A non-inferiority trial found that hydroxychloroquine and pioglitazone had comparable antihyperglycemic efficacy [58•]. In addition, a small retrospective cohort study of adults with diabetes and rheumatologic disease compared those treated with hydroxychloroquine versus methotrexate and found that hydroxychloroquine was associated with a significantly greater reduction in HbA1c from pre-treatment baseline to its lowest value within 12 months of initiating treatment [59].

Hydroxychloroquine has also been found to prevent incident diabetes in adults with rheumatologic disease in four large cohort studies. These studies did not distinguish between incident type 1 and type 2 diabetes, though most cases were likely type 2 given the participants' age. The first of these studies was a prospective cohort of patients with RA with a study duration of 21.5 years which found an adjusted hazard ratio (aHR) for incident diabetes of 0.62 (95 % CI 0.42, 0.92) in those prescribed hydroxychloroquine versus other RA treatments [60]. A retrospective cohort study of patients with RA with a median follow-up time of 2 years found an aHR for incident diabetes of 0.29 (95 % CI 0.09, 0.95) in ever versus never users of hydroxychloroquine [61]. Similarly, a retrospective cohort study of patients with RA or psoriasis with a median follow-up time of 6 months found an aHR for incident diabetes of 0.54 (95 % CI 0.36, 0.80) in those prescribed hydroxychloroquine versus other disease-modifying drugs excluding TNF inhibitors [62]. In these three studies, the outcome was adjusted for prior glucocorticoid use as a binary categorical variable. A recent retrospective cohort study of patients with systemic lupus erythematosus with a mean follow-up time of 5.6 years found an aHR for incident diabetes of 0.26 (95 % CI 0.18, 0.37) in those with cumulative hydroxychloroquine dose ≥129 g (compared to those never prescribed hydroxychloroquine), adjusted for daily glucocorticoid dose in four categories [63•]. A cross-sectional study of non-diabetic women with rheumatologic disease found that hydroxychloroquine was associated with lower fasting glucose [64].

Relatively, little is known about the effects of hydroxychloroquine on patients with autoimmune diabetes. Since hydroxychloroquine is suspected to augment the response to insulin in target tissues, we would expect it to result in reduced exogenous insulin needs. In

addition, rat models of endocrine pancreatic failure have demonstrated that hydroxychloroquine inhibits inflammatory cytokines and protects against beta cell loss [65•]. One case report describes a patient with type 1 diabetes who experienced improved glycemic control after hydroxychloroquine was started to treat Sjogren's syndrome [66].

Leflunomide

Leflunomide is an inhibitor of pyrimidine synthesis that is used for RA and off-label for several rheumatologic diseases [1, 67]. No studies were found for effects of leflunomide on diabetes.

Methotrexate

Methotrexate is a synthetic folate analog that inhibits DNA synthesis at chemotherapeutic doses, but at lower rheumatologic doses, exerts anti-inflammatory effects by several metabolic mechanisms [68]. It is first-line therapy for RA and juvenile idiopathic arthritis (JIA) and is used off-label for a variety of rheumatologic conditions [1]. There is little evidence of effects of methotrexate on diabetes, and the available evidence suggests that there are no significant effects. A small retrospective cohort study of patients with diabetes and rheumatologic disease treated with hydroxychloroquine versus methotrexate found no significant change in HbA1c from baseline in either group (though a significantly larger decrease in HbA1c in the hydroxychloroquine group) [59]. In a retrospective cohort study of non-diabetic patients with RA or psoriasis, methotrexate was not significantly associated with a reduction of incident diabetes (aHR 0.77, 95 % CI 0.53, 1.13) [62].

Minocycline

Minocycline is a tetracycline antibiotic that has anti-inflammatory properties and is used to treat mild RA [1, 69]. No studies were found for effects of minocycline on diabetes.

Mycophenolate Mofetil

Mycophenolate mofetil is the prodrug of mycophenolic acid which inhibits purine salvage, suppressing the proliferation of T and B lymphocytes [70]. It is used off-label to treat a variety of rheumatologic conditions [1, 71]. There is evidence that mycophenolate mofetil has no significant effects on type 1 diabetes; no studies were found for effects on type 2 diabetes nor diabetes prevention. An RCT of mycophenolate mofetil without and with the interleukin-2 blocking antibody daclizumab in patients with recent onset type 1 diabetes found no effect of either intervention on SCP, HbA1c, or insulin dose at 2 years [72]. There is one case report of mycophenolate mofetil being helpful in treating a patient with profound insulin resistance due to high levels of anti-insulin antibodies [73].

Sulfasalazine

Sulfasalazine is a compound with sulfonamide and salicylate moieties that exerts anti-inflammatory effects by multiple mechanisms [74]. It is first-line therapy for mild to moderate RA and JIA and has several off-label rheumatologic uses [1]. Like dapsone, sulfasalazine frequently causes hemolysis [75] that can falsely lower HbA1c measurements [39, 40]. There is one case report of a patient with type 1 diabetes who developed spuriously

low HbA1c values after sulfasalazine was initiated for treatment of RA [76]. One study identified patients with diabetes who had taken sulfasalazine and found that their HbA1c values were dramatically lower when taking the drug, concluding that sulfasalazine has glucose-lowering effects [77]. However, hemolysis was not evaluated in these patients, making it impossible to determine whether the reduced HbA1c reflected hemolysis or a true change in blood glucose.

TNF Inhibitors

Tumor necrosis factor (TNF) inhibitors are monoclonal antibodies (except etanercept which is an immunoglobulin fusion protein) that suppress the action of TNF-α, a proinflammatory cytokine [78]. They are approved to treat RA, psoriatic arthritis, ankylosing spondylitis, and JIA and have many off-label rheumatologic uses [1, 78].

In 2009, an RCT was conducted of etanercept versus placebo in children with recent onset type 1 diabetes which found that etanercept increased SCP and decreased HbA1c and insulin dose at 6 months [79]. Although there are no other trials of TNF inhibitors for diabetes treatment, there are case reports of patients with autoimmune diabetes who experienced improved glycemic control and/or hypoglycemia after initiating treatment with etanercept [80, 81], adalimumab [82–84], and infliximab [85], suggesting that the effects of etanercept on type 1 diabetes are generalizable to TNF inhibitors as a group. Of note, there are two reported cases of type 1 diabetes developing shortly after TNF inhibitors were started, raising the concern that TNF inhibitors were the cause [86, 87]. An increased incidence of type 1 diabetes or secondary autoimmune diseases was not specifically found in trials of TNF inhibitors, though the degree to which this outcome was reported is unclear [88].

There is evidence suggesting that TNF inhibitors may improve glycemic control in patients with type 2 diabetes. A retrospective study identified eight patients with type 2 diabetes and RA or Crohn disease who were treated with etanercept or infliximab and found significantly lower fasting glucose after TNF inhibitor treatment, unlike control patients treated with other medications [89]. There are case reports of patients with type 2 diabetes who experienced improved glycemic control and/or hypoglycemia after treatment with etanercept [90–93] and adalimumab [83], and one patient who was able to stop insulin therapy during infliximab treatment and then relapsed after infliximab was withdrawn [94, 95].

Furthermore, there is evidence that treatment with TNF inhibitors reduces the risk of incident diabetes in patients with rheumatologic disease. A large retrospective cohort study of patients with RA or psoriasis with a median follow-up time of 6 months found an aHR for incident diabetes of 0.62 (95 % CI 0.42, 0.91) in patients prescribed TNF inhibitors versus other disease-modifying drugs excluding hydroxychloroquine [62]. This study adjusted for glucocorticoid use as a binary categorical variable and did not differentiate between incident type 1 and type 2 diabetes, though most cases were likely type 2 given participant age.

Abatacept

Abatacept is an immunoglobulin fusion protein that blocks T lymphocyte co-stimulation and resultant T cell activation [96]. It is used to treat RA, JIA, and off-label for psoriatic arthritis [1]. In 2011, an RCT was conducted of abatacept for recent onset type 1 diabetes which

found that abatacept increased SCP and decreased HbA1c at 2 years, with no effect on insulin dose [97]. Significant improvements in SCP and HbA1c were still present 1 year after abatacept was discontinued [98•]. No studies were found of effects of abatacept on type 2 diabetes or diabetes prevention.

Alefacept

Alefacept is an immunoglobulin fusion protein that blocks T lymphocyte co-stimulation and reduces circulating memory T cells [99]. It is used for psoriasis and off-label to treat psoriatic arthritis [100]. In 2015, an RCT was conducted of alefacept for recent onset type 1 diabetes which found that alefacept increased SCP and decreased insulin dose and major hypoglycemic events at 2 years, with no effect on HbA1c [13]. No studies were found of effects of alefacept on type 2 diabetes nor diabetes prevention.

Anakinra and Canakinumab

Anakinra and canakinumab are biologic agents that inhibit the inflammatory cytokine, IL-1 [101]. Anakinra is used to treat RA, and canakinumab is used off-label for several rheumatologic conditions [101]. Anakinra and canakinumab were each examined as a potential treatment for recent onset type 1 diabetes by the same group in 2013 and were found to have no effect on SCP, HbA1c, or insulin dose [102•]. A small study with no control group found that a short course of anakinra in overweight patients with type 1 diabetes resulted in modestly improved HbA1c and fasting glucose [103].

There is some evidence that IL-1 inhibitors have antihyperglycemic effects in patients with type 2 diabetes. An RCT of overweight adults (body mass index > 27 kg/m^2) with type 2 diabetes found that anakinra decreased HbA1c by 0.46% (95 % CI 0.01%, 0.90%) more than placebo at 13 weeks [104], with no difference in HbA1c after treatment was withdrawn [105]. Additionally, there is a case series of two patients with type 2 diabetes who experienced improved glycemic control after anakinra was started for RA [106]. A phase II trial of canakinumab in patients with type 2 diabetes found no significant improvements in glycemic control relative to placebo [107].

Rituximab

Rituximab is a monoclonal antibody that targets and depletes B lymphocytes [108]. It is used to treat RA, certain vasculitides, and off-label for several rheumatologic diseases [1]. In 2009, an RCT was conducted of rituximab for recent onset type 1 diabetes which found that rituximab weekly for 4 weeks increased SCP and decreased HbA1c and insulin dose at 1 year [109]. There was no significant difference in these outcomes 1 year after treatment was withdrawn [110]. There is one case report of a patient with type 1 diabetes who experienced improved glycemic control after starting rituximab for immune thrombocytopenia [111]. No studies were found of effects of rituximab on type 2 diabetes or diabetes prevention.

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that targets the proinflammatory cytokine IL-6 which is used to treat RA and JIA [112]. There is little evidence of effects of tocilizumab on diabetes. One prospective study of ten patients with type 2 diabetes initiating

treatment with tocilizumab for RA found that HbA1c decreased by 0.82% 1 month after starting treatment and before steroids were tapered; however, there was no relevant control group [113].

Conclusions

The effects of immune modulators on pancreatic function in patients with autoimmune diabetes have implications for treatment selection for rheumatologic indications. Preserving pancreatic function has important long-term benefits to patients with type 1 diabetes including reducing microvascular complications and hypoglycemic events [114, 115]. However, most studies of immune modulators have been performed in patients with type 1 diabetes of recent onset. The effects of these drugs on pancreatic function in patients with autoimmune diabetes of longer duration, as will most commonly be seen in clinical practice, are not known. Due to the progressive nature of autoimmune pancreatic destruction, we would expect the efficacy of immune modulators to decrease with longer diabetes duration. However, there is heterogeneity in the natural history of type 1 diabetes and adequate beta cell function may persist for many years in a subset of patients [116]. In addition, patients with slowly progressing type 1 diabetes or LADA have a weaker autoimmune process and maintain greater pancreatic function over time [117]. It is possible that immune modulators would have greater benefit in this population, though there is no clear evidence substantiating this to date. Overall, in selecting an immune modulator for rheumatologic use, evidence of improved pancreatic function could be considered as a potential benefit to patients with autoimmune diabetes. Given the limited data on long-term diabetes outcomes, we do not recommend selecting an immune modulator for rheumatologic use solely because of diabetes benefits that would otherwise be undesirable due to known adverse effects.

Immune modulators with antihyperglycemic effects should be considered for rheumatologic indications in patients with type 2 diabetes or type 2 diabetes risk factors. In patients with difficult to control hyperglycemia, hydroxychloroquine may be preferred for rheumatologic use due to its consistent benefits on glycemic control. In patients at high risk of developing type 2 diabetes due to histories of prediabetes, gestational diabetes, obesity, or chronic corticosteroid use, hydroxychloroquine or a TNF inhibitor should be considered for rheumatologic use due to evidence of diabetes prevention. The preference for these medications in patients at high cardiovascular risk is further supported by studies demonstrating that hydroxychloroquine improves lipid profiles [56, 58•, 118, 119], and TNF inhibitors are associated with a lower rate of cardiovascular events in patients with RA [120]. Most studies of diabetes prevention by immune modulators are limited by simplistic modeling of glucocorticoid use as a binary categorical variable which likely created residual confounding. Further studies are needed to confirm that the effects of immune modulators on diabetes prevention are independent of their steroid sparing effects.

Starting or switching immune-modulating medications is a high-risk period for changes in diabetes disease activity that places patients at risk for hypoglycemia. Of note, the glycemic effects of immune modulators may not be immediate: in trials of recent onset type 1 diabetes, effects on pancreatic function often did not become apparent until after at least 3 months of therapy. In these trials, changes in glycemic control were expected and

participants were monitored closely to match their pancreatic function and insulin needs. Likewise, practitioners prescribing immune-modulating drugs should plan for changes in glycemic control by partnering with the patient and their care team. Patients should be informed of the risk of hypoglycemia and empowered to contact providers promptly for trends in home glucose or insulin needs. Practitioners treating diabetes should be made aware of changes in immune-modulating therapy so that they may coordinate care.

Patients taking dapsone or sulfasalazine require an alternative method of glycemic monitoring other than HbA1c. Prior to initiating therapy with dapsone or sulfasalazine, patients with diabetes should be switched to monitoring with fructosamine or glycated albumin [39]. In addition, patients on these medications who require screening for type 2 diabetes should be screened with fasting serum glucose on two occasions or a 2-h oral glucose tolerance test [121].

There is a need for further study of the effects of immune modulators on diabetes-related outcomes. In order to guide treatment in patients with rheumatologic disease, it will be essential to define more clearly the comparative effectiveness of these medications on long-term outcomes, specifically cardiovascular disease, microvascular disease, and mortality. In patients with autoimmune diabetes, it will be important to determine whether immune modulators will benefit those who have not been recently diagnosed, and whether they will be more effective at improving pancreatic function in patients with LADA who have a more indolent autoimmune process. Patients with rheumatologic disease provide an excellent opportunity for prospective studies of immune modulators as there is already an indication for treatment, and the prevalence of diabetes is relatively high. Collaboration between providers in the fields of rheumatology and diabetes care will make further studies in this area possible.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

• Of major importance

1. Imboden, JB., Hellmann, DB., Stone, JH. Current diagnosis and treatment rheumatology. 3. New York: McGraw-Hill Medical; 2012.
2. Somers EC, Thomas SL, Smeeth L, Hall AJ. Are individuals with an autoimmune disease at higher risk of a second auto-immune disorder? Am J Epidemiol. 2009; 169(6):749–55. DOI: 10.1093/aje/kwn408 [PubMed: 19224981]
3. Liao KP, Gunnarsson M, Kallberg H, Ding B, Plenge RM, Padyukov L, et al. Specific association of type 1 diabetes mellitus with anti-cyclic citrullinated peptide-positive rheumatoid arthritis. Arthritis Rheum. 2009; 60(3):653–60. DOI: 10.1002/art.24362 [PubMed: 19248096]
4. Han C, Robinson DW Jr, Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol. 2006; 33(11):2167–72. [PubMed: 16981296]
5. Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis. 2005; 64(11):1595– 601. DOI: 10.1136/ard.2004.034777 [PubMed: 15843450]

6. von Herrath M, Sanda S, Herold K. Type 1 diabetes as a relapsing-remitting disease? Nat Rev Immunol. 2007; 7(12):988–94. DOI: 10.1038/nri2192 [PubMed: 17982429]
7. Aly H, Gottlieb P. The honeymoon phase: intersection of metabolism and immunology. Curr Opin Endocrinol Diabetes Obes. 2009; 16(4):286–92. DOI: 10.1097/MED.0b013e32832e0693 [PubMed: 19506474]
8. Mortensen HB, Hougaard P, Swift P, Hansen L, Holl RW, Hoey H, et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. Diabetes Care. 2009; 32(8):1384–90. DOI: 10.2337/dc08-1987 [PubMed: 19435955]
9. Agner T, Damm P, Binder C. Remission in IDDM: prospective study of basal C-peptide and insulin dose in 268 consecutive patients. Diabetes Care. 1987; 10(2):164–9. [PubMed: 3556104]
10. Waldron-Lynch F, Herold KC. Immunomodulatory therapy to preserve pancreatic beta-cell function in type 1 diabetes. Nat Rev Drug Discov. 2011; 10(6):439–52. DOI: 10.1038/nrd3402 [PubMed: 21629294]
11. Bach JF, Chatenoud L. A historical view from thirty eventful years of immunotherapy in autoimmune diabetes. Semin Immunol. 2011; 23(3):174–81. DOI: 10.1016/j.smim.2011.07.009 [PubMed: 21846589]
12. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. Diabetes. 2004; 53(1):250–64. [PubMed: 14693724]
13••. Rigby MR, Harris KM, Pinckney A, DiMeglio LA, Rendell MS, Felner EI, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. J Clin Invest. 2015; 125(8):3285–96. This trial demonstrates that alafecept has beneficial effects on recent onset type 1 diabetes with no increase in adverse events. DOI: 10.1172/JCI81722 [PubMed: 26193635]
14. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. Eur J Clin Pharmacol. 2008; 64(8):753–67. DOI: 10.1007/s00228-008-0478-6 [PubMed: 18506437]
15. Silverstein J, Maclaren N, Riley W, Spillar R, Radjenovic D, Johnson S. Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. N Engl J Med. 1988; 319(10):599–604. DOI: 10.1056/NEJM198809083191002 [PubMed: 3045545]
16. Cook JJ, Hudson I, Harrison LC, Dean B, Colman PG, Werther GA, et al. Double-blind controlled trial of azathioprine in children with newly diagnosed type I diabetes. Diabetes. 1989; 38(6):779–83. [PubMed: 2656346]
17. Harrison LC, Colman PG, Dean B, Baxter R, Martin FI. Increase in remission rate in newly diagnosed type I diabetic subjects treated with azathioprine. Diabetes. 1985; 34(12):1306–8. [PubMed: 3905463]
18. Moncada E, Subira ML, Oleaga A, Goni F, Sanchez-Ibarrola A, Monreal M, et al. Insulin requirements and residual beta-cell function 12 months after concluding immunotherapy in type I diabetic patients treated with combined azathioprine and thymostimulin administration for one year. J Autoimmun. 1990; 3(5):625–38. [PubMed: 2252531]
19. Slobodnick A, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: old and new. Am J Med. 2015; 128(5):461–70. DOI: 10.1016/j.amjmed.2014.12.010 [PubMed: 25554368]
20. Das UN. Colchicine in diabetes mellitus. J Assoc Physicians India. 1993; 41(4):213. [PubMed: 8270561]
21. Wang L, Sawhney M, Zhao Y, Carpio GR, Fonseca V, Shi L. Association between colchicine and risk of diabetes among the veterans affairs population with gout. Clin Ther. 2015; 37(6):1206–15. DOI: 10.1016/j.clinthera.2015.03.010 [PubMed: 25857595]
22. Magnasco A, Rossi A, Catarsi P, Gusmano R, Ginevri F, Perfumo F, et al. Cyclosporin and organ specific toxicity: clinical aspects, pharmacogenetics and perspectives. Curr Clin Pharmacol. 2008; 3(3):166–73. [PubMed: 18781903]
23. The Canadian-European Randomized Trial Group. Cyclosporin-induced remission of IDDM after early intervention. Association of 1 yr of cyclosporin treatment with enhanced insulin secretion. Diabetes. 1988; 37(11):1574–82. [PubMed: 2903105]

24. Skyler JS, Rabinovitch A, Group MCDS. Cyclosporine in recent onset type I diabetes mellitus. Effects on islet beta cell function. J Diabetes Complications. 1992; 6(2):77–88. [PubMed: 1611143]
25. Chase HP, Butler-Simon N, Garg SK, Hayward A, Klingensmith GJ, Hamman RF, et al. Cyclosporine A for the treatment of new-onset insulin-dependent diabetes mellitus. Pediatrics. 1990; 85(3):241–5. [PubMed: 2304776]
26. Feutren G, Papoz L, Assan R, Vialettes B, Karsenty G, Vexiau P, et al. Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset. Results of a multicentre double-blind trial. Lancet. 1986; 2(8499):119–24. [PubMed: 2873396]
27. O'Brien D, Butler N, Chase HP, Hammon R, Hayward A, Klingensmith G, et al. Cyclosporin A in treatment of new-onset type I diabetes mellitus. Diabetes Care. 1988; 11(3):297.
28. Dupre J, Stiller CR, Gent M, Donner A, von Graffenreid B, Murphy G, et al. Effects of immunosuppression with cyclosporine in insulin-dependent diabetes mellitus of recent onset: the Canadian open study at 44 months. Transplant Proc. 1988; 20(3 Suppl 4):184–92. [PubMed: 3289204]
29. Stiller CR, Dupre J, Gent M, Jenner MR, Keown PA, Laupacis A, et al. Effects of cyclosporine immunosuppression in insulin-dependent diabetes mellitus of recent onset. Science. 1984; 223(4643):1362–7. [PubMed: 6367043]
30. Bougneres PF, Carel JC, Castano L, Boitard C, Gardin JP, Landais P, et al. Factors associated with early remission of type I diabetes in children treated with cyclosporine. N Engl J Med. 1988; 318(11):663–70. DOI: 10.1056/NEJM198803173181103 [PubMed: 3125434]
31. Sobel DO, Henzke A, Abbassi V. Cyclosporin and methotrexate therapy induces remission in type 1 diabetes mellitus. Acta Diabetol. 2010; 47(3):243–50. DOI: 10.1007/s00592-010-0188-2 [PubMed: 20440520]
32. Fleming RA. An overview of cyclophosphamide and ifosfamide pharmacology. Pharmacotherapy. 1997; 17(5 Pt 2):146S–54S. [PubMed: 9322882]
33. Henderson RG, Rubens RD. Cyclophosphamide and diabetes. Cancer Chemother Pharmacol. 1981; 5(3):207. [PubMed: 7028303]
34. Chang DJ, Lamothe M, Stevens RM, Sigal LH. Dapsone in rheumatoid arthritis. Semin Arthritis Rheum. 1996; 25(6):390–403. [PubMed: 8792511]
35. Degowin RL, Eppes RB, Powell RD, Carson PE. The haemolytic effects of diaphenylsulfone (DDS) in normal subjects and in those with glucose-6-phosphate-dehydrogenase deficiency. Bull World Health Organ. 1966; 35(2):165–79. [PubMed: 5297001]
36. Halim NK, Ogbeide E. Haematological alterations in leprosy patients treated with dapsone. East Afr Med J. 2002; 79(2):100–2. [PubMed: 12380888]
37. Lee I, Barton TD, Goral S, Doyle AM, Bloom RD, Chojnowski D, et al. Complications related to dapsone use for Pneumocystis jirovecii pneumonia prophylaxis in solid organ transplant recipients. Am J Transplant. 2005; 5(11):2791–5. DOI: 10.1111/j.1600-6143.2005.01079.x [PubMed: 16212642]
38. Barclay JA, Ziemba SE, Ibrahim RB. Dapsone-induced methemoglobinemia: a primer for clinicians. Ann Pharmacother. 2011; 45(9):1103–15. DOI: 10.1345/aph.1Q139 [PubMed: 21852596]
39. Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med. 2014; 29(2):388–94. DOI: 10.1007/s11606-013-2595-x [PubMed: 24002631]
40. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. J Diabetes. 2009; 1(1):9–17. DOI: 10.1111/j.1753-0407.2009.00009.x [PubMed: 20923515]
41. Albright ES, Ovalle F, Bell DS. Artificially low hemoglobin A1c caused by use of dapsone. Endocr Pract. 2002; 8(5):370–2. DOI: 10.4158/EP.8.5.370 [PubMed: 15259122]
42. Lai YC, Wang CS, Wang YC, Hsu YL, Chuang LM. Falsely decreased HbA1c in a type 2 diabetic patient treated with dapsone. J Formos Med Assoc. 2012; 111(2):109–12. DOI: 10.1016/j.jfma.2012.01.007 [PubMed: 22370290]

43. Roxby A, Jain R. Dapsone interferes with hemoglobin A1c monitoring of diabetes in an HIV-infected patient. AIDS. 2013; 27(2):299–301. DOI: 10.1097/QAD.0b013e32835adde8 [PubMed: 23238555]
44. Shah AD, Fox RK, Rushakoff RJ. Falsely decreased HbA1c in a type 2 diabetic patient treated with dapsone. Endocr Pract. 2014; 20(11):e229–32. DOI: 10.4158/EP14291.CR [PubMed: 25100400]
45. van Vollenhoven RF. Corticosteroids in rheumatic disease. Understanding their effects is key to their use. Postgrad Med. 1998; 103(2):137–42. [PubMed: 9479312]
46. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Minambres I, Gomez-Huelgas R. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014; 6(1):9–20. DOI: 10.1111/1753-0407.12090 [PubMed: 24103089]
47•. Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. Ann Nutr Metab. 2014; 65(4):324–32. This is a meta-analysis of the incidence of hyperglycemia and new-onset diabetes due to glucocorticoids in non-diabetic patients. DOI: 10.1159/000365892 [PubMed: 25402408]
48. Mistura L, Beccaria L, Meschi F, Flores D'Arcais A, Pellini C, Puzzovio M, et al. Prednisone treatment in newly diagnosed type I diabetic children: 1-yr follow-up. Diabetes Care. 1987; 10(1): 39–43. [PubMed: 3552513]
49. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993; 23(2 Suppl 1):82–91. [PubMed: 8278823]
50. Olsen NJ, Schleich MA, Karp DR. Multifaceted effects of hydroxychloroquine in human disease. Semin Arthritis Rheum. 2013; 43(2):264–72. DOI: 10.1016/j.semarthrit.2013.01.001 [PubMed: 23481418]
51. Cansu DU, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. Rheumatology (Oxford). 2008; 47(3):378– 9. DOI: 10.1093/rheumatology/kem378 [PubMed: 18222983]
52. Winter EM, Schrander-van der Meer A, Eustatia-Rutten C, Janssen M. Hydroxychloroquine as a glucose lowering drug. BMJ Case Rep. 2011; doi: 10.1136/bcr.06.2011.4393
53. Kang L, Mikuls TR, O'Dell JR. Hydroxychloroquine: a diabetic drug in disguise? BMJ Case Rep. 2009; doi: 10.1136/bcr.08.2008.0654
54. Shojania K, Koehler BE, Elliott T. Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis. J Rheumatol. 1999; 26(1):195–6. [PubMed: 9918262]
55. Unubol M, Ayhan M, Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. J Clin Rheumatol. 2011; 17(1):46–7. DOI: 10.1097/RHU.0b013e3182098e1f [PubMed: 21169846]
56. Gerstein HC, Thorpe KE, Taylor DW, Haynes RB. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas—a randomized trial. Diabetes Res Clin Pract. 2002; 55(3):209–19. [PubMed: 11850097]
57. Quatraro A, Consoli G, Magno M, Caretta F, Nardozza A, Ceriello A, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? Ann Intern Med. 1990; 112(9):678–81. [PubMed: 2110430]
58•. Pareek A, Chandurkar N, Thomas N, Viswanathan V, Deshpande A, Gupta OP, et al. Efficacy and safety of hydroxychloroquine in the treatment of type 2 diabetes mellitus: a double blind, randomized comparison with pioglitazone. Curr Med Res Opin. 2014; 30(7):1257–66. This trial compares hydroxychloroquine to pioglitazone in patients with type 2 diabetes demonstrating non-inferiority of hydroxychloroquine in reducing HbA1c, and improved lipid profiles in the hydroxychloroquine arm. DOI: 10.1185/03007995.2014.909393 [PubMed: 24669876]
59. Rekedal LR, Massarotti E, Garg R, Bhatia R, Gleeson T, Lu B, et al. Changes in glycosylated hemoglobin after initiation of hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. Arthritis Rheum. 2010; 62(12):3569–73. DOI: 10.1002/art.27703 [PubMed: 20722019]
60. Wasko MC, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. JAMA. 2007; 298(2):187–93. DOI: 10.1001/jama.298.2.187 [PubMed: 17622600]

61. Bili A, Sartorius JA, Kirchner HL, Morris SJ, Ledwich LJ, Antohe JL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol. 2011; 17(3): 115–20. DOI: 10.1097/RHU.0b013e318214b6b5 [PubMed: 21441823]

62. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying anti-rheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA. 2011; 305(24):2525–31. DOI: 10.1001/jama.2011.878 [PubMed: 21693740]

63•. Chen YM, Lin CH, Lan TH, Chen HH, Chang SN, Chen YH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. Rheumatology (Oxford). 2015; 54(7):1244–9. This retrospective cohort study found lower diabetes incidence associated with higher exposure to hydroxychloroquine in patients with systemic lupus erythematosus using a nation-wide registry in Taiwan. DOI: 10.1093/rheumatology/keu451 [PubMed: 25587177]

64. Penn SK, Kao AH, Schott LL, Elliott JR, Toledo FG, Kuller L, et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 2010; 37(6):1136–42. DOI: 10.3899/jrheum.090994 [PubMed: 20436082]

65•. Abdel-Hamid AA, El-Firgany Ael D. Hydroxychloroquine hindering of diabetic isletopathy carries its signature on the inflammatory cytokines. J Mol Histol. 2016; 47(2):183–93. This study examines the histologic and immunologic effects of hydroxychloroquine in a rat models of pancreatic endocrine failure. DOI: 10.1007/s10735-016-9664-5 [PubMed: 26872459]

66. Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. Ther Adv Endocrinol Metab. 2014; 5(4):77–85. DOI: 10.1177/2042018814547204 [PubMed: 25343023]

67. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2000; 59(11):841–9. [PubMed: 11053058]

68. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev. 2005; 57(2):163–72. DOI: 10.1124/pr.57.2.3 [PubMed: 15914465]

69. Garrido-Mesa N, Zarzuelo A, Galvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013; 169(2):337–52. DOI: 10.1111/bph.12139 [PubMed: 23441623]

70. Allison AC. Mechanisms of action of mycophenolate mofetil. Lupus. 2005; 14(Suppl 1):s2–8. [PubMed: 15803924]

71. Iaccarino L, Rampudda M, Canova M, Della Libera S, Sarzi-Puttinic P, Doria A. Mycophenolate mofetil: what is its place in the treatment of autoimmune rheumatic diseases? Autoimmun Rev. 2007; 6(3):190–5. DOI: 10.1016/j.autrev.2006.11.001 [PubMed: 17289556]

72. Gottlieb PA, Quinlan S, Krause Steinrauf H, Greenbaum CJ, Wilson DM, Rodriguez H, et al. Failure to preserve beta-cell function with mycophenolate mofetil and daclizumab combined therapy in patients with new-onset type 1 diabetes. Diabetes Care. 2010; 33(4):826–32. DOI: 10.2337/dc09-1349 [PubMed: 20067954]

73. Segal T, Webb EA, Viner R, Pusey C, Wild G, Allgrove J. Severe insulin resistance secondary to insulin antibodies: successful treatment with the immunosuppressant MMF. Pediatr Diabetes. 2008; 9(3pt1):250–4. DOI: 10.1111/j.1399-5448.2008.00408.x [PubMed: 18547238]

74. Smedegard G, Bjork J. Sulphasalazine: mechanism of action in rheumatoid arthritis. Br J Rheumatol. 1995; 34(Suppl 2):7–15. [PubMed: 8535652]

75. Taffet SL, Das KM. Sulfasalazine. Adverse effects and desensitization. Dig Dis Sci. 1983; 28(9): 833–42. [PubMed: 6136396]

76. Tack CJ, Wetzels JF. Decreased HbA1c levels due to sulfonamide-induced hemolysis in two IDDM patients. Diabetes Care. 1996; 19(7):775–6. [PubMed: 8799639]

77. Haas RM, Li P, Chu JW. Glucose-lowering effects of sulfasalazine in type 2 diabetes. Diabetes Care. 2005; 28(9):2238–9. [PubMed: 16123497]

78. Jin J, Chang Y, Wei W. Clinical application and evaluation of anti-TNF-alpha agents for the treatment of rheumatoid arthritis. Acta Pharmacol Sin. 2010; 31(9):1133–40. DOI: 10.1038/aps.2010.134 [PubMed: 20711219]

79. Mastrandrea L, Yu J, Behrens T, Buchlis J, Albini C, Fourtner S, et al. Etanercept treatment in children with new-onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study. Diabetes Care. 2009; 32(7):1244–9. DOI: 10.2337/dc09-0054 [PubMed: 19366957]

80. Montes VN, Hirsch IB. Treatment of LADA with etanercept. Diabetes Care. 2012; 35(5):e36.doi: 10.2337/dc12-0128 [PubMed: 22517944]
81. Olivieri AN, Iafusco D, Mellos A, Zanfardino A, Mauro A, Granato C, et al. Refractory rheumatoid factor positive polyarthritis in a female adolescent already suffering from type 1 diabetes mellitus and Hashimoto's thyroiditis successfully treated with etanercept. Ital J Pediatr. 2013; 39:64.doi: 10.1186/1824-7288-39-64 [PubMed: 24124913]
82. Boulton JG, Bourne JT. Unstable diabetes in a patient receiving anti-TNF-alpha for rheumatoid arthritis. Rheumatology (Oxford). 2007; 46(1):178–9. DOI: 10.1093/rheumatology/kel322 [PubMed: 16998233]
83. van Eijk IC, Peters MJ, Nurmohamed MT, van Deutekom AW, Dijkmans BA, Simsek S. Decrease of fructosamine levels during treatment with adalimumab in patients with both diabetes and rheumatoid arthritis. Eur J Endocrinol. 2007; 156(3):291–3. DOI: 10.1530/EJE-06-0693 [PubMed: 17322487]
84. Arif S, Cox P, Afzali B, Lombardi G, Lechler RI, Peakman M, et al. Anti-TNFalpha therapy—killing two birds with one stone? Lancet. 2010; 375(9733):2278.doi: 10.1016/S0140-6736(10)60394-7 [PubMed: 20609973]
85. Timper K, Hruz P, Beglinger C, Donath MY. Infliximab in the treatment of Crohn disease and type 1 diabetes. Diabetes Care. 2013; 36(7):e90–1. DOI: 10.2337/dc13-0199 [PubMed: 23801815]
86. Bloom BJ. Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum. 2000; 43(11):2606–8. DOI: 10.1002/1529-0131(200011)43:11<2606::AID-ANR31>3.0.CO;2-X [PubMed: 11083287]
87. Tack CJ, Kleijwegt FS, Van Riel PL, Roep BO. Development of type 1 diabetes in a patient treated with anti-TNF-alpha therapy for active rheumatoid arthritis. Diabetologia. 2009; 52(7):1442–4. DOI: 10.1007/s00125-009-1381-0 [PubMed: 19440690]
88. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011; 2:CD008794.doi: 10.1002/14651858.CD008794.pub2
89. Gupta-Ganguli M, Cox K, Means B, Gerling I, Solomon SS. Does therapy with anti-TNF-alpha improve glucose tolerance and control in patients with type 2 diabetes? Diabetes Care. 2011; 34(7):e121.doi: 10.2337/dc10-1334 [PubMed: 21709287]
90. Farrokhi F, Taylor HC, McBride NM. Etanercept-induced hypo-glycemia and improved glycemic control in a patient with type 2 diabetes. Endocr Pract. 2011; 17(2):306–7. [PubMed: 21474422]
91. Cheung D, Bryer-Ash M. Persistent hypoglycemia in a patient with diabetes taking etanercept for the treatment of psoriasis. J Am Acad Dermatol. 2009; 60(6):1032–6. DOI: 10.1016/j.jaad.2008.12.012 [PubMed: 19217693]
92. Wambier CG, Foss-Freitas MC, Paschoal RS, Tomazini MV, Simao JC, Foss MC, et al. Severe hypoglycemia after initiation of anti-tumor necrosis factor therapy with etanercept in a patient with generalized pustular psoriasis and type 2 diabetes mellitus. J Am Acad Dermatol. 2009; 60(5):883–5. DOI: 10.1016/j.jaad.2008.10.009 [PubMed: 19389539]
93. Bonilla E, Lee YY, Phillips PE, Perl A. Hypoglycaemia after initiation of treatment with etanercept in a patient with type 2 diabetes mellitus. Ann Rheum Dis. 2007; 66(12):1688.doi: 10.1136/ard.2007.072256 [PubMed: 17998221]
94. Yazdani-Biuki B, Stelzl H, Brezinschek HP, Hermann J, Mueller T, Krippl P, et al. Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-alpha antibody infliximab. Eur J Clin Invest. 2004; 34(9):641–2. DOI: 10.1111/j.1365-2362.2004.01390.x [PubMed: 15379764]
95. Yazdani-Biuki B, Mueller T, Brezinschek HP, Hermann J, Graninger W, Wascher TC. Relapse of diabetes after interruption of chronic administration of anti-tumor necrosis factor-alpha antibody infliximab: a case observation. Diabetes Care. 2006; 29(7):1712–3. DOI: 10.2337/dc06-0636 [PubMed: 16801612]
96. Herrero-Beaumont G, Martinez Calatrava MJ, Castaneda S. Abatacept mechanism of action: concordance with its clinical profile. Reumatol Clin. 2012; 8(2):78–83. DOI: 10.1016/j.reuma.2011.08.002 [PubMed: 22104048]

97. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 378(9789):412–9. DOI: 10.1016/S0140-6736(11)60886-6 [PubMed: 21719096]

98•. Orban T, Bundy B, Becker DJ, Dimeglio LA, Gitelman SE, Goland R, et al. Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment. Diabetes Care. 2014; 37(4):1069–75. This follow-up study to an RCT of abatacept in recent onset type 1 diabetes [97] demonstrates persistent improvements in pancreatic function one year after abatacept was stopped. DOI: 10.2337/dc13-0604 [PubMed: 24296850]

99. Chamian F, Lin SL, Lee E, Kikuchi T, Gilleaudeau P, Sullivan-Whalen M, et al. Alefacept (anti-CD2) causes a selective reduction in circulating effector memory T cells (Tem) and relative preservation of central memory T cells (Tcm) in psoriasis. J Transl Med. 2007; 5:27.doi: 10.1186/1479-5876-5-27 [PubMed: 17555598]

100. Scheinfeld N. Alefacept: its safety profile, off-label uses, and potential as part of combination therapies for psoriasis. J Dermatolog Treat. 2007; 18(4):197–208. DOI: 10.1080/09546630701247955 [PubMed: 17671880]

101. Cavalli G, Dinarello CA. Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. Rheumatology (Oxford). 2015; 54(12):2134– 44. DOI: 10.1093/rheumatology/kev269 [PubMed: 26209330]

102•. Moran A, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet. 2013; 381(9881):1905–15. This trial of anakinra or canakinumab versus placebo finds no effects on pancreatic function of either drug in patients with recent onset type 1 diabetes. DOI: 10.1016/S0140-6736(13)60023-9 [PubMed: 23562090]

103. van Asseldonk EJ, van Poppel PC, Ballak DB, Stienstra R, Netea MG, Tack CJ. One week treatment with the IL-1 receptor antagonist anakinra leads to a sustained improvement in insulin sensitivity in insulin resistant patients with type 1 diabetes mellitus. Clin Immunol. 2015; 160(2): 155–62. DOI: 10.1016/j.clim.2015.06.003 [PubMed: 26073226]

104. Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 2007; 356(15):1517–26. DOI: 10.1056/NEJMoa065213 [PubMed: 17429083]

105. Larsen CM, Faulenbach M, Vaag A, Ehses JA, Donath MY, Mandrup-Poulsen T. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. Diabetes Care. 2009; 32(9): 1663–8. DOI: 10.2337/dc09-0533 [PubMed: 19542207]

106. Ruscitti P, Cipriani P, Cantarini L, Liakouli V, Vitale A, Carubbi F, et al. Efficacy of inhibition of IL-1 in patients with rheumatoid arthritis and type 2 diabetes mellitus: two case reports and review of the literature. J Med Case Rep. 2015; 9:123.doi: 10.1186/s13256-015-0603-y [PubMed: 26033326]

107. Hensen J, Howard CP, Walter V, Thuren T. Impact of interleukin-1beta antibody (canakinumab) on glycaemic indicators in patients with type 2 diabetes mellitus: results of secondary endpoints from a randomized, placebo-controlled trial. Diabetes Metab. 2013; 39(6):524–31. DOI: 10.1016/j.diabet.2013.07.003 [PubMed: 24075453]

108. Weiner GJ. Rituximab: mechanism of action. Semin Hematol. 2010; 47(2):115–23. DOI: 10.1053/j.seminhematol.2010.01.011 [PubMed: 20350658]

109. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009; 361(22):2143–52. DOI: 10.1056/NEJMoa0904452 [PubMed: 19940299]

110. Pescovitz MD, Greenbaum CJ, Bundy B, Becker DJ, Gitelman SE, Goland R, et al. B-lymphocyte depletion with rituximab and beta-cell function: two-year results. Diabetes Care. 2014; 37(2): 453–9. DOI: 10.2337/dc13-0626 [PubMed: 24026563]

111. Quintana L, Paniagua JA, Gil-Contreras D, Jimenez-Yuste V, Torres A, Velasco F. Improving type 1 diabetes after treatment of immune thrombocytopenia with rituximab: killing two birds with one stone. Diabetes Care. 2010; 33(9):e122.doi: 10.2337/dc10-0959 [PubMed: 20805264]

112. Tanaka T, Narazaki M, Kishimoto T. Anti-interleukin-6 receptor antibody, tocilizumab, for the treatment of autoim-mune diseases. FEBS Lett. 2011; 585(23):3699–709. DOI: 10.1016/j.febslet.2011.03.023 [PubMed: 21419125]

113. Ogata A, Morishima A, Hirano T, Hishitani Y, Hagihara K, Shima Y, et al. Improvement of HbA1c during treatment with humanised anti-interleukin 6 receptor antibody, tocilizumab. Ann Rheum Dis. 2011; 70(6):1164–5. DOI: 10.1136/ard.2010.132845 [PubMed: 20980285]

114. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care. 2003; 26(3):832–6. [PubMed: 12610045]

115. Panero F, Novelli G, Zucco C, Fornengo P, Perotto M, Segre O, et al. Fasting plasma C-peptide and micro- and macrovascular complications in a large clinic-based cohort of type 1 diabetic patients. Diabetes Care. 2009; 32(2):301–5. DOI: 10.2337/dc08-1241 [PubMed: 19017769]

116. Coppieters KT, Dotta F, Amirian N, Campbell PD, Kay TW, Atkinson MA, et al. Demonstration of islet-autoreactive CD8 T cells in insulitic lesions from recent onset and long-term type 1 diabetes patients. J Exp Med. 2012; 209(1):51–60. DOI: 10.1084/jem.20111187 [PubMed: 22213807]

117. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, et al. Immunogenetic and clinical characterization of slowly progressive IDDM. Diabetes Care. 1993; 16(5):780–8. [PubMed: 8098691]

118. Morris SJ, Wasko MC, Antohe JL, Sartorius JA, Kirchner HL, Dancea S, et al. Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients. Arthritis Care Res (Hoboken). 2011; 63(4):530–4. DOI: 10.1002/acr.20393 [PubMed: 21452265]

119. Solomon DH, Garg R, Lu B, Todd DJ, Mercer E, Norton T, et al. Effect of hydroxychloroquine on insulin sensitivity and lipid parameters in rheumatoid arthritis patients without diabetes mellitus: a randomized, blinded crossover trial. Arthritis Care Res (Hoboken). 2014; 66(8):1246–51. DOI: 10.1002/acr.22285 [PubMed: 24470436]

120. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005; 32(7):1213–8. [PubMed: 15996054]

121. Association AD. Standards of medical care in diabetes—2014. Diabetes Care. 2014; 37(Suppl 1):S14–80. DOI: 10.2337/dc14-S014 [PubMed: 24357209]

Table 1

Effects on diabetes of rheumatologic immune modulators: evidence from RCTs and large cohort studies

Drug	Effects on autoimmune diabetes	Effects on type 2 diabetes	Effects on diabetes prevention
Non-biologic agents			
Azathioprine	In recent onset T1DM: no effect on FCP, SCP, HbA1c, insulin dose [16]. With prednisone, ↑ SCP and ↓ insulin dose [15].	No studies.	No studies.
Colchicine	No studies.	No studies.	Does not prevent incident diabetes [21].
Cyclosporine	In recent onset T1DM: ↑ SCP in most studies, no consistent effect on HbA1c and insulin dose [23–27].	No studies.	No studies.
Cyclophosphamide	No studies.	No studies.	No studies.
Dapsone[a]	No studies.	No studies.	No studies.
Glucocorticoids	↑ Hyperglycemia [46]. With azathioprine in recent onset T1DM, ↑ SCP and ↓ insulin dose [15].	↑ Hyperglycemia [46].	Causes incident diabetes [47].
Hydroxychloroquine	No studies, but suspected to decrease insulin needs.	↓ HbA1c [56, 57, 58•].	Prevents incident diabetes in patients w/rheumatologic disease [60–62, 63•].
Leflunomide	No studies.	No studies.	No studies.
Methotrexate	No studies.	No studies.	Does not prevent incident diabetes in patients w/rheumatologic disease [62].
Minocycline	No studies.	No studies.	No studies.
Mycophenolate mofetil	In recent onset T1DM: no effect on SCP, HbA1c, insulin [72].	No studies.	No studies.
Sulfasalazine [a]	No studies.	No studies.	No studies.
TNF Inhibitors	Etanercept in recent onset T1DM: ↑ SCP, ↓ HbA1c and insulin dose [79].	No studies.	Prevent incident diabetes in patients with rheumatologic disease [62].
Other Biologic Agents			
Abatacept	In recent onset T1DM: ↑ SCP, ↓ HbA1c, no change in insulin dose [97].	No studies.	No studies.
Alefacept	In recent onset T1DM: ↑ SCP, ↓ insulin dose, ↓ hypoglycemia,no change in HbA1c [13••].	No studies.	No studies.
Anakinra	In recent onset T1DM: no effect on SCP, HbA1c, insulin dose [102•].	Modestly ↓HbA1c in those with BMI > 27 kg/m^2 [104].	No studies.
Canakinumab	In recent onset T1DM: no effect on SCP, HbA1c, insulin dose [102•].	No effect on HbA1c in a phase II trial [107].	No studies.
Rituximab	In recent onset T1DM: ↑ SCP, ↓ HbA1c and insulin dose [109].	No studies.	No studies.
Tocilizumab	No studies.	No studies.	No studies.

FCP fasting C-peptide, *SCP* stimulated C-peptide, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes

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[a]May falsely lower HbA1c by effects on erythrocytes