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Immunology of Multiple Sclerosis

Regina Berkovich

Introduction

This author proposes to approach the subject of immunology of multiple sclerosis (MS) from the standpoint of available acute and disease-modifying therapies (DMTs) and currently known immunologic targets for them.

This seems to be a sound approach because historically this vision point has helped to shape and direct our knowledge on MS immunology and has developed and enriched the field over the years.

Another good reason to adopt this approach is its immediate applicability. By engaging this view, we learn not only MS immunology but also how various different medications work. And we not only learn how they work (in other words, mechanism of action or MoA of DMTs) but also come very close to understanding their potential efficacy, risks, and side effects. This strategic approach will serve well in understanding emerging MS therapies.

Unlike many other diseases of the immune system, such as lupus, psoriasis, or rheumatoid arthritis, MS has a single target, and that is myelin. Therefore, we do not expect to see multiple different tissues involved—the

immune system and central nervous system (CNS) are the fields where the events take place.

Contrary to many patients' beliefs, MS is not a disease of a "weak" immune system; it is a disease of a mistaken immune system. In fact, immune reactions in MS can prove to be very strong, leading to remarkable CNS inflammatory reactions and subsequent damage. But the initial "intentions" of the activated immune system are "good"; it intends to "protect" the human, the host. There is a hypothesis of strong initial inflammatory reaction, which leads to cascades of delayed events in the immune system; for example, one may have had an episode of acute infection, such as, for example, mononucleosis, which made a particularly strong and lasting impression on the immune system, and ever since that episode the immune system gets itself activated trying to find the offending agent, virus or bacteria, for weeks, months, or even years and decades after this particular infection is over. The overzealous protective efforts may get so intense that even mere resemblance to the offending antigen (e.g., the encounter of biochemical structures similar to the structures of relevant viral molecules) may be sufficient to trigger a very strong and destructive immune reaction. The most acute form of inflammation in MS clinically presents itself as a relapse or exacerbation.

Particular environmental factors may predispose to ongoing immune reactions to produce the disease. In addition to the aforementioned infectious exposure, lower levels of vitamin D, increased salt intake, genetic predisposition, obesity, and tobacco exposure seem to contribute to the process.

Initially intended as a protective mechanism, reactive inflammation fails to curb itself to a reasonable or adequate intensity, and chronic progressive disease develops.

As mentioned earlier, the singular target in MS is myelin represented specifically in the CNS, and MS is one of the most prominent CNS demyelinating conditions.

As the term suggests, demyelination is the key component of this disease. As you recall, myelin is a layer of "insulation" surrounding the central nerve fiber or axon. Every fragment of myelin is built by several layers of a single oligodendrocyte, a CNS cell that rolls its own body and membranes around the axon multiple times, thus creating the myelin. It is remarkable that myelin of the CNS is principally different from that of the peripheral nervous system; the latter is built by Schwann cells and the peripheral myelin is not a target for MS. Therefore, peripheral neuropathies are rarely seen in patients with MS, unless those are comorbid or in other words independently developed. As a side note: remember that the only "nerve" directly involved in MS is the optic nerve, but it is not a peripheral nerve per se; it is in fact a "continuation" or "processes" of the brain.

Destruction of myelin is a result of inflammation, which can be acute, subacute, and/or chronic. The three conditions can overlap and coexist. Acute inflammation tends to coincide with the first event of MS or subsequent MS relapses (acute exacerbation) and/or new, active, or enlarged MS lesion formation. Events leading to inflammation targeting myelin usually start outside of the CNS and where the main representation of immune system tends to be, in hematolymphatic system. Mature activated lymphocytes in their search of a potential target encounter the blood-brain barrier (BBB) and gain an increasingly strong ability to cross it; subsequently, they enter the CNS. Activation of the lymphocytes and increased permeability of the BBB result from antigen presentation by the antigen-presenting cells, increased production of proinflammatory cytokines, involvement of the complement cascade, and increased differentiation of activated aggressive lymphocytes.

Thus, the activation of the immune process is initiated systematically, resulting in migration of activated immune cells into the CNS where they get reactivated and their interactions result in parenchymal inflammation; the acute inflammation in MS may be focal, multifocal, or diffuse and is characterized by infiltration of activated lymphocytes, macrophages, and microglia, with involvement of cortex, white matter, and deep gray matter with myelin destruction; axonal, neuronal, and synaptic loss; astroglial reaction; remyelination; and synaptic rearrangement.

Indeed, the experimental studies on the intimate mechanisms of action of the approved or developing drugs for relapsing-remitting MS (RRMS) provide a strong foundation for understanding the immunology of MS. Deregulated immune response, including inflammatory cells (e.g., T cells, B cells, macrophages) and immune mediators (e.g., cytokines, chemokines, matrix metalloproteinases, complement), contributes to the expansion of autoreactive T cells; proinflammatory shifts promote BBB lymphocyte and monocyte extravasation. It was found that activation of B cells of patients with MS may contribute to increased BBB permeability. Regulatory T cells (Tregs) normally control the intensity of an immune response; however, their regulatory function in patients with MS is dramatically impaired. Remarkably, the immunomodulatory role of Tregs and their suppressive capacity are more affected in the early stages of the disease. Consistent with this, there are differences in function and expression of FOXP3 (a master regulator in the development and function of regulatory T cells). Disease exacerbation of MS is also associated with loss of the differentiated autoregulatory CD8+ T cells. The regulatory cell dysfunction in patients with RRMS is especially profound during MS exacerbations as compared with the remission periods or in healthy controls. It was observed that, for example, proinflammatory Th17 cell expansion in patients with MS is counterbalanced by an expanded CD39+ regulatory T cell population during remission but not during relapse. Regulatory B cell (Bregs) subsets were found to be higher during relapse as compared

with patients with non–clinically active MS. There is a growing body of evidence that antibodies play an important role in the pathobiology of MS and MS relapse; IgG antibodies purified from a patient with MS and transferred to mice with experimental autoimmune encephalomyelitis caused a dramatic clinical improvement during relapse after selective IgG removal, whereas passive transfer of patient's IgG exacerbated motor deficits in animals. These data provide evidence for a previously unknown mechanism involved in immune regulation in acute MS.

Destruction of myelin leads to exposure and increased vulnerability of the axons. According to the data by Bruce Trapp, the number of transected axons increases with the level of activity in MS lesions, and in active MS lesions can be more than 11,000. Transected axons indicate permanent damage. Conglomerates of transected axons form permanent CNS lesions, which subsequently advance the brain tissue volume loss.

Brain tissue loss is the strongest morphologic correlate with MS disability progression. Therefore, the famous sentence "time is brain" so actively and successfully used in stroke neurology has its specific relevance to MS as well, with the only difference that, in stroke, time means minutes and hours and in MS, time means weeks and months. The sentiment, however, is the same: Do not delay the start of treatment.

As mentioned earlier, the knowledge on MS immunology grew together with the continuous and ongoing introduction of different DMTs for MS treatment. The mechanism of action of different treatments for MS targets specific "key players" as discussed earlier.

Let us review the **targets**.

Blood-Brain Barrier

As we remember, increased permeability of the BBB allows activated aggressive lymphocytes to travel from the bloodstream and into the CNS (brain, spinal cord, or optic nerves).

High-dose systemic steroids and **adrenocorticotrophic hormone,** two Food and Drug Administration (FDA)-approved options for immediate treatment of MS relapse, are known to dramatically reduce the BBB permeability among their other direct and indirect anti-inflammatory functions, helping them to significantly shorten prolongation of disturbing symptoms associated with MS exacerbation.

While we are on this relevant subject, let us discuss specifically the specifics of MS relapse treatment.

Relapses (exacerbations, attacks, or flares) are a hallmark of MS and are often associated with significant functional impairment and decreased health-related quality of life. For the vast majority of patients with MS, relapses are the central concern and provoke most of the fears and uncertainty associated with the disease. The unpredictability of MS exacerbations only adds to the notoriety of this entity.

The generally accepted definition of an MS exacerbation is a new or worsening neurologic deficit lasting 24 hours or more, in the absence of fever or infection.

The symptoms associated with MS relapse represent activation of any demyelinating lesion or lesions located in any segment of the CNS; therefore, there may be a broad variety of different signs (which may or may not replicate previously experienced episodes).

In general, the most commonly seen symptom complexes are related to new or worsened inflammatory processes involving the optic nerves, spinal cord, cerebellum, and/or cerebrum. Thus, the symptoms may present alone or as a combination of visual disturbances, motor and sensory impairments, balance issues, and cognitive deficits.

It is important to rule out symptoms that mimic exacerbations but that do not represent new damage to the nervous system. These pseudoexacerbations are caused by an uncovering of older symptoms due to Uhthoff phenomenon (overheating shortens the duration of action potentials, leading to electrochemical transmission failure along demyelinated axons); common causes include fever, infections (most commonly seen urinary tract and upper respiratory infections), and exposure to significant temperature extremes.

Usually the natural course of most of MS exacerbations completes itself with a period of repair leading to clinical remission and, sometimes, especially early in the disease course, to a complete recovery; however, the residual deficit after an MS relapse may persist and contribute to the stepwise progression of disability.

There are many reasons to treat an MS relapse:

1. Treatment of MS relapses is important because it may help to shorten and lessen the disability associated with it.
2. Successful treatment of MS relapse has another important psychological aspect: it helps to establish good physician-patient relationship and to develop in patients with MS a feeling of trust that they may be able to take control over their disease.

The history of acute relapse treatment in MS reflects well the history of what we know about MS and how the knowledge evolved. In the early 20th century, the treatment of choice for an acute MS relapse was bed rest. In 1978, the first medication for MS relapse treatment was approved—adrenocorticotropic hormone, or ACTH.

The presumption that the efficacy of ACTH gel results solely from its corticotropic effects later led to the acceptance of high-dose corticosteroids for MS exacerbation treatment. However, more recent data in other disease states (e.g., nephrotic syndrome, opsoclonus-myoclonus, and infantile spasms) provide clinical evidence that steroidogenic actions fail to fully explain the efficacy of ACTH gel in these conditions. In addition, research into melanocortin peptides and their receptors argues against the

long-standing belief that the beneficial effect of ACTH depends solely on its ability to stimulate the release of endogenous corticosteroids and suggests that further exploration of how best to use ACTH in MS should be considered. The melanocortin system has many diverse functions in the human body, including melanogenesis, glucocorticoid production, control of food intake and energy expenditure, control of sexual function, behavioral effects, attention, memory, learning, and, important for MS, neuroprotection, immune modulation, and anti-inflammatory effects. The description of the melanocortin system and the recognition of the other proposed mechanisms of action of ACTH may help to explain the renewed interest in ACTH.

As mentioned previously, in the 1980s focus shifted to intravenous methylprednisolone (IVMP) as the preferred treatment option for MS relapse.

Low dosages of systemic steroids were found to be ineffective in MS, and the dosages from 500 mg to 1 g of IVMP per day became widely accepted and the preferred regimen.

Ever since ACTH and corticosteroids have been used to treat MS relapses, it was observed that some cases may not respond to these treatment options.

Several alternatives, including plasmapheresis, cyclophosphamide, or intravenous immunoglobulin were attempted, but it seems that only the plasmapheresis option is supported by strong evidence. In 2011, American Academy of Neurology guidelines recommended **plasmapheresis** for severe MS exacerbations not responding to the first-line treatments.

Summary and Practical Recommendations

Adequate diagnosis of MS relapses is essential.

Mild exacerbations may not require steroid treatment.

There is a general consensus that moderate to severe MS exacerbations with disabling symptoms should be treated using high-dose systemic steroids (intravenous or oral).

- Patients suspected to have a possible relapse should be evaluated within a week (or 5 working days) of the new or worsening symptom onset;
- If MS relapse is confirmed, start the treatment as soon as possible;
- IVMP 1 g per day for 3 to 5 days is generally recommended as a first choice.

Although not FDA approved, oral administration of high-dose MP may be suggested.

Patients with MS relapse, who did not respond or did not tolerate the MP, may be offered another FDA-approved option—ACTH. Given as ACTH gel, it should be administered either intramuscularly or subcutaneously (SQ) 80 units a day for at least 5 days and up to 10 to 15 days.

For patients with disabling MS relapse symptoms not responding to either systemic steroids or ACTH, plasmapheresis should be considered as an every other day procedure to a total of up to seven exchanges.

Historically, MS relapse therapies were first introduced for MS treatment back in the 1970s. At that time, the general understanding was that RRMS is immunologically active mostly during relapses and remissions are the opposite state, not or much less associated with inflammation. This view, however, failed to explain the polyphasic nature of MS, with acute exacerbations being born within the time of seemingly peaceful remissions.

The growing need for relapse prevention presented itself. The new disease-modification approach arrived.

Indeed, the DMTs are medications that modify the course of a chronic progressive disease such as MS, ideally improving its long-term prognosis as compared with the natural history of untreated MS.

The very first DMT introduced back in 1993, interferon **(IFN)-beta-1B** or **Betaseron** (SQ every other day), along with other **beta-IFN-1As,** such as **Avonex, Rebif,** and **Plegridy**, modulate the immune system in MS and as a part of their anti-inflammatory action regulate and eventually normalize permeability of the BBB. These have been associated with significant reduction of MS relapses and also with reduction of new and active magnetic resonance imaging (MRI) lesions.

The class of **beta-IFNs** were developed after the initial unsuccessful attempts to study gamma-IFNs for MS treatment. The theory stemmed from the known antiviral properties of the IFNs and understanding of the potential role of infectious (likely viral ones) in the triggering of MS debut. However, the gamma-IFNs proved to be harmful and in fact were shown to exacerbate MS. In contrast, the beta-IFNs, which were studied next, had shown strong anti-inflammatory effects in MS, believed to be caused at least partly by regulating the BBB permeability and partly by peripheral and central direct and indirect shifts in immune system with results favoring a less inflammatory state. Betaseron became historically the very first DMT for MS approved and broadly used. Its extensive clinical research has shown positive results in both clinical and MRI metrics. The participants of the very first pivotal study of Betaseron in MS DMT were evaluated 21 years later and were found to have a significantly higher chance of being alive two decades later as compared with their placebo counterparts.

The most common side effects of the beta-IFNs are, predictably, flulike symptoms, well-known symptoms associated with inner IFN production that we all have a chance to experience during flu seasons as sufferers from upper respiratory viral infections. Importantly, in patients with MS with other autoimmune conditions, such as lupus, autoimmune thyroiditis, or neuromyelitis optica, the beta-IFN treatment results may not be positive because of their alternative immune reactions with more antibody-driven and interleukin 17 immunity tendencies, and therefore in such individuals IFNs should be avoided. Finally, it needs to be stated that, even though the decreased permeability of the BBB seems to play

an important role in the MoA of beta IFNs, the action is rather regulatory and not absolute, and therefore, although significant clinical and MRI results are achieved, no CNS opportunistic infections were ever observed or reported. The beta-IFNs are considered truly immunomodulatory DMTs with a favorable safety profile of variable tolerability.

Another great example of MS medication classically being associated with the function of the BBB is one of the very robust and potent DMTs, **natalizumab or Tysabri** (intravenously [IV] every 4 wk). It blocks the adhesion molecule on the surface of the lymphocytes, preventing their trafficking through the BBB and into the CNS. This results in the unique opportunity of significant reduction of CNS inflammation, which translates into a dramatic reduction of relapse frequency, stopping or significantly slowing the disability progression and strong MRI results demonstrating a significant reduction in active and newly developed MS lesions. The action of cell redistribution is so powerful that even minimally physiologically necessary number of lymphocytes do not seem to be able to cross the BBB, which, unfortunately, predisposes some patients to opportunistic brain infection, such as progressive multifocal leukoencephalopathy (PML). The overall estimated risk of PML in patients administered Tysabri is relatively small, between 1:10,000 and 1:1000. However, prolonged use of Tysabri, previous use of immunosupressants, and exposure to the JC virus (JCV) are the three factors that are known to increase the risk of PML so that in worst circumstances it can approach roughly 1%. Patients with MS who have never been previously exposed to natalizumab are in the spectrum of significantly lower risk of PML, even though some of them may have been previously exposed to the JCV (in fact, more than half of adult population has been previously exposed to the JCV, which in individuals with preserved immune system does not cause a disease). If, in addition, these natalizumab-naive patients never had previously been treated with immunosuppressants such as chemotherapy, then such individuals have one single risk factor of the three known and their PML risk is still relatively low. Importantly, simple discontinuation of natalizumab results in restoration of the BBB permeability within few weeks (around 50-60 d); this can be significantly speeded up by administering of plasmapheresis, which can rapidly remove natalizumab from the system. This reversibility of the immunologic effect of natalizumab and the absence of associated lymphopenia seem to support the opinion that natalizumab is an immunomodulatory drug rather than an immunosuppressive one, although the fact of associated opportunistic infection such as PML tends to suggest the opposite viewpoint maintaining its potentially immunosuppressive character.

Importantly, following discontinuation of Tysabri the restoration of the baseline BBB permeability may be associated with the prompt return of aggressive lymphocytes increasingly trafficking into the CNS and with the return of MS activity, sometimes referred to as “MS rebound.” If discontinuation of natalizumab (Tysabri) seems to be necessary, the prescriber

needs to have a sound "exit strategy" to assure firm control over otherwise potentially serious possibility of returned MS activity.

Another way of decreasing trafficking of aggressive lymphocytes into the CNS is to minimize their presence in the circulating blood by capturing those cells in lymphoid organs such as lymph nodes. The medications doing just that are the **S1P receptor modulators** such as **fingolimod (Gilenya**, oral once a day) and siponimod. The S1P receptor is needed to establish free exit of lymphocytes from the lymph nodes; once it is blocked, the cells end up being sequestered inside of the lymphoid tissues, and their presence in the peripheral blood drops dramatically. In fact, one may expect to see the mere three-digit numbers of circulating lymphocytes as assessed by the absolute lymphocyte counts (ALCs) of the complete blood count test. In spite this seemingly severe lymphopenia, the patient is not expected to experience frequent or unusually severe infections (one should monitor for oneself nevertheless); it has been proposed that the factual ALC number does not represent the true state of immune surveillance and may in fact be so-called pseudolymphopenia. Nevertheless, rare cases of opportunistic infections uniquely associated with fingolimod have been reported, including coccideomycosis and PML. It appears that two possible risk factors here are the patient's advanced age and length of fingolimod exposure; remarkably, the level of lymphocytes and degree of lymphopenia are not among the risk factors.

Higher or lower selectivity of S1P receptor inhibition in different existing and upcoming DMTs of this class may call for less or more laborious screening pretreatment tests, which include electrocardiography, eye examination to rule out macular edema, laboratory tests, and observation following the administration of the first dose. Furthermore, it is important to keep in mind that those individuals not immune to the varicella zoster virus need to be vaccinated to prevent serious systemic zoster infections. Fingolimod is classified as an immunomodulatory drug by the FDA, and indeed, once discontinued, the status quo of the immune system gets restored within 6 to 8 weeks back to the pretreatment baseline levels. This supports the notion that lymphocytes indeed get released from the lymph nodes where they were previously sequestered and do not merely get reproduced, which would have required a significantly longer time.

Myelin

Myelin itself is undoubtedly a key player in MS pathology. One DMT that developed out of the copolymer strikingly resembling the myelin basic protein structure is called glatiramer acetate (GA) or Copaxone (SQ every day or three times a week).

An interesting fact is that initially the molecule was introduced with the hope to help create a better animal model for MS. It was expected to induce MS-like disease in rodents. It is remarkable that, in fact, animals seem to be much better protected by nature from MS-like conditions, and

therefore, researchers are always looking into better ways to model MS in animals. Thus, the copolymer was hoped to induce more robust MS-like events in animals by being structurally close to myelin. Instead, it repeatedly showed the opposite action. Not only was it not inducing the expected demyelination but in fact it was preventing it from developing and was treating the existing one. After several more years of laborious research and development GA was born and approved. It is assumed that its MoA modulates the immune system via series of different events in the periphery and in the CNS resulting in a more anti-inflammatory immune climate. The resemblance to the myelin basic protein may play a role in what has been hypothesized as possible vaccinelike effects. As we see, however, the BBB function does not seem to have a major role here. Because of this we may need to be aware of a few things: less robust effects with less impressive MRI results and also no risk of PML or other opportunistic infections.

Free Radicals

Dimethyl fumarate (DMF) (Tecfidera, oral twice a day) is believed to work by regulating the free radical formation that is involved in inflammatory reactions, and by doing so the DMF creates a less inflammatory environment in the systems, including the CNS. The medication does not seem to be active on the level of the BBB, and therefore, immediate robust clinical and MRI effects should not be expected; however, an early start and monitored response may place this DMT among good options for the first-line and early second-line use. Some individuals may run into a problem of lymphopenia, and because it is impossible to predict who is more likely to be prone to it, the ALC levels of every patient administered Tecfidera needs to be checked at least every 6 months, with discontinuation recommended with an ALC below 500 cells. Neglect to follow this recommendation may predispose lymphopenic patients to opportunistic infections, including PML.

Common side effects include flushing episodes and gastrointestinal symptoms, which may create certain tolerability and compliance issues, but once persevered tend to dissipate with time.

Overall, all three oral therapies can be used as first-line or second-line agents.

These three drugs do not have similar mechanisms and associated risks; the only thing they have in common is that all three are oral drugs. The three should be approached differently.

Cells

In previous sections, as we discussed the role of the BBB permeability, the phenomenon of sequestration, and the shifts in immunologic states we already mentioned the lymphocytes. Now we will see how the immune status can get affected by direct targeting of lymphocytes and their reproductive mechanisms.

Let us start with the DMT that causes a less dramatic impact on the cell counts and is associated with no or very rare absolute lymphopenia. **Teriflunomide (Aubagio**, oral daily) blocks a specific mitochondrial enzyme dehydroorotatedehydrogenase, which is involved in the reproduction of fast-developing activated lymphocytes, which account for less than 15% of functional lymphocytes. One therefore expects to see not more than 15% of ALC drop, which indeed is a fact. The ALC in a patient administered Aubagio in general is expected to remain within the normal range. The cases of lymphopenia are extremely rare. The opportunistic infections uniquely associated with Aubagio have not been reported. The common infection rate is close to that of the placebo group. No specific cancer signal was observed. The medication was classified by the FDA as an immunomodulatory drug. Teriflunomide demonstrates a clinical and MRI efficacy comparable with that of the high-dose high-frequency injectable IFNs, arguably the stronger ones in their class, as it has been compared head-to-head with Rebif. It has the convenience of oral administration, good tolerability, and compliance. In addition, it is the only oral DMT at this point demonstrating reproducible effects in preventing disability progression in two independent clinical trials. It can be rapidly eliminated from the system by administration of activated charcoal or cholestiramin orally for 11 days, a useful property for the patients desiring to get pregnant.

B Lymphocyte Depletion

Here we will discuss ocrelizumab (Ocrevus), which is FDA approved for RRMS and primary progressive MS, and rituximab (Rituxan), which is used off-label. Both are used IV roughly every 6 months continuously.

The theory behind the use of the B cell depletion is the increasingly recognized role of B lymphocytes in MS pathology. They not only serve as antigen-presenting cells but also act as active producers of immunoglobulins and play an important role in various humoral immune reactions getting more recognized in the MS process. The medications are clearly classified by the FDA as immunosuppressive drugs. Indeed, once the drug is discontinued, it may require many months and even (in the case of ocrelizumab) longer than a year to see the resurgence of newly developed B cells. Removing the important player of MS pathology—B lymphocytes—results in significant clinical and MRI results, affording these DMTs the well-deserved place among high-efficacy MS medications. It comes as no surprise that high efficacy frequently associates with higher risks. In this particular class, to understand the specific risks we need to look closer into the fundamental role of B lymphocytes in the immune defense. As mentioned previously, they develop into antibody-producing cells. Depletion of B cells leads to decreased antibody production, which may result in deficiencies in anti-infectious and anticancerogenic surveillance activities.

Depletion Followed by Reproduction

We discussed previously that MS is a disease of mistaken immune system. Clearly, the natural reaction would be to attempt to fix the mistake. And many DMTs we discussed earlier attempt to fix the errors of the immune system on variably peripheral levels by blocking the immediate results of the pathological immune reactions. The DMTs we are about to review now tend to attempt to get closer to the root of the problem, to the very production of the immune cells. In a nutshell, the idea is to reprogram the immune system from the very level of bone marrow cell differentiation. Alemtuzumab (Lemtrada, IV, +_two courses 12 mo apart) is the only currently approved DMT of this class. Designed to recognize and destroy the mature circulating T and B lymphocytes predominantly, it causes profound acute lymphopenia, which by itself dramatically stimulates the bone marrow into urgent production of new lymphocytes. The newly reproduced lymphocytes then get destroyed again by the second course of treatment 12 months later, and the process of reproduction repeats itself. Most patients with MS were shown to get into long-term remission induced just by the two initial treatment courses. This DMT, clearly recognized by the FDA as an immunosupressive drug, is among, if not the, strongest MS medication. The associated risks are direct results of the unique MoA. The above-mentioned cell reproduction starts with the resurgence of much faster reproduced B cells, which may predispose patients to the development of certain antibody-driven autoimmune complications, such as Grave disease, idiopathic thrombocytopenia, and more rare autoimmune nephropathies. Although these potential complications are treatable, they should be diagnosed as early as possible. The monitoring requires monthly blood and urine tests for 4 years following the last Lemtrada infusion (REMS program). Even though this drug is approved in the European Union as a first-line DMT (given its great and proven promise of long-lasting MS remission), in the United States it is generally recommended after two tried and failed DMTs. Probably because the lymphopenia caused by alemtuzumab is not long lasting, it has not been associated with PML and there is no specific cancer signal.

Summary

We reviewed several pharmacologic targets and a majority of available specific DMTs (Table 2.1).

We discussed the **beta-IFNs** and **glatiramer acetate**, which are frequently combined into one section as **injectable DMTs**. Indeed, they all need to be injected, as their molecules are fragile and get destroyed in the gastric tract. Another common feature is that they all are **immunomodulatory** and as such are not associated with opportunistic infections or

TABLE 2.1
DISEASE-MODIFYING THERAPIES AND ADVERSE EVENTS AND TARGETS OF ACTION

Product	Teriflunomide	Fingolimod	Dimethyl Fumarate (DMF)	IFNβ-1a, IFNβ-1b, PEG IFNβ-1a	Glatiramer Acetate
Brief MoA	Immunomodulatory agent ■ Inhibits DHODH enzyme ■ Reduces number of activated T and B lymphocytes in CNS	■ S1P receptor modulator ■ High affinity for SIP 1, 3, 4, 5 ■ Blocks capacity of lymphocytes to egress from lymph nodes, reducing number of lymphocytes in peripheral blood, which may reduce lymphocyte migration into CNS	■ DMF activates Nrf2 pathway, which is involved in cellular response to oxidative stress	■ Affects antigen presentation to drive T helper cells into an anti-inflammatory state, increase activity of regulatory T and B lymphocytes, and reduce the abilities of B cells to act as antigen-presenting cells	■ Modifies immune processes believed to be responsible for the pathogenesis of MS. Studies in animals and in vitro systems show induction and activation of specific suppressor T cells in the periphery
PML Warning	**No**	**Yes**	**Yes**	**No**	**No**
Contraception	**Required**	**Required**	**Required**	**Required**	**Required**
Side Effects	Headache, ↑ALT, diarrhea, hair thinning, and nausea	Headache, ↑LFTs, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity, macular edema	Flushing, abdominal pain, diarrhea, and nausea	Flulike symptoms, injection site reactions, ↑LFTs, thrombotic microangiopathy seizures, depression	Injection site reactions, chest pain, rash, dyspnea, vasodilatation, urticaria, hypersensitivity, lipoatrophy

(Continued)

TABLE 2.1
DISEASE-MODIFYING THERAPIES AND ADVERSE EVENTS AND TARGETS OF ACTION (CONTINUED)

Monitoring	■ Before starting: CBC, LFT, TB test, blood pressure ■ After starting: monthly LFT × 6 mo, periodic BP monitoring	■ Monitor ECG before and for 6 h after starting first dose in a setting that can readily manage symptomatic bradycardia ■ Others: monitor heart rate, CBC, pulmonary function test, liver enzymes, and BP	■ Before starting: CBC, LFTs ■ After starting: CBC after 6 mo, then every 6-12 mo, and as clinically indicated. Obtain LFTs as clinically indicated ■ Consider interrupting treatment in patients with lymphocyte counts <500, persisting more than 6 mo ■ Discontinue treatment if there is clinically significant liver injury	■ CBC, LFTs at 1, 3, 6 mo ■ Thyroid function tests	No laboratory monitoring required

ALT, alanintransferase; BP, blood pressure; CBC, complete blood count; CNS, central nervous system; DHODH, dehydroorotatedehydrogenase; ECG, electrocardiography; IFN, interferon; LFT, liver functional tests; MoA, mechanism of action; MS, multiple sclerosis; PEG, polyethylene glycol; PML, progressive multifocal leukoencephalopathy; TB, tuberculosis.

cancer signals. The injectables (beta-IFNs and glatiramer acetate) have been around since 1990s, are well known, and tend to be viewed as safe. A careful physician needs to reassess their efficacy on a regular basis, using clinical and MRI parameters, as not every patient with MS will respond to them even after a period of initial success (but this, admittedly, is relevant to all DMTs). Injectables are commonly used as a first-line DMT and at times as a second-line DMT, although the later becomes less common in the light of newer DMTs.

Furthermore, we discussed **oral DMTs**, specifically **fingolimod**, **teriflunomide**, and **dimethyl fumarate**.

A good exercise to check your understanding of one important issue with different DMTs is self-assessment on potential lymphopenia.

Let us look into this.

- Recall that lymphopenia is rare with immunomodulatory DMTs such as injectables and teriflunomide. In a majority of patients, the ALC remains within normal limits.
- Recall that lymphopenia is very dramatic and common with fingolimod, because this is exactly how this drug works—by shifting the lymphocytes from the circulating blood into the lymph nodes, an action known as sequestration. A low ALC should not be expected in the setting of fingolimod use (and the drug should not be associated with an increased risk of infections) and is being viewed by many experts as pseudo lymphopenia.
- Finally, recall that the ALC numbers seen in the setting of DMF use actually represent the real numbers, and therefore, if lymphopenia is seen, it is for real and the DMF needs to be discontinued if the ALC drops below 500 cells.

Finally, we discussed the **infusible DMTs natalizumab**, **ocrelizumab**, and **alemtuzumab**, which, despite having strikingly different MoAs and risk profiles, all are recognized as **high-efficacy DMTs**.

They tend to be used earlier in patients with MS with unfavorable prognostic indicators, such as highly active clinical course of MS; frequent and severe relapses; faster disability accumulation including early presentation of motor, cerebellar, and sphincter deficits; male patients; and patients of ethnic minority for MS (African Americans, Asians, Hispanics).

It is important to remember that both ocrelizumab and alemtuzumab are immunosuppressive agents. Therefore, if the plan is to use natalizumab at some point, it should be positioned before any immunosupressive drugs to minimize the potential PML risks.

Although infusible DMTs can be used as a first-line agent in cases of highly active MS, they are frequently used as second- and third-line agents in those patients with MS who tried and failed other less risky DMTs.

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