1. Introduction

The treatment of multiple sclerosis (MS) is entering a new era, characterized by the availability of a broad range of disease modifying drugs (DMDs) for patients in the relapsing-remitting (RR) phase of the disease. Through interference with immune-mediated inflammatory processes the DMDs reduce the number and severity of relapses and the increase in relapse-related disability. Each DMD is characterized by a unique combination of mode of action, route of administration, degree of efficacy and potential side effects. In the past two decades the injectable drugs interferon beta-1a (INFb-1a), INFb-1b and glatiramer acetate (GA) have been proven to be safe first-line treatments. In more recent years, the intravenously administered monoclonal antibody natalizumab and the oral drugs fingolimod and cladribine have been demonstrated to be efficacious in RRMS. These DMDs are more potent, but also potentially more hazardous, which by and large restricts their use to patients who have very active disease or are refractory to first-line treatment. Lately, phase II/III studies showed beneficial effects of the oral drugs teriflunomide, laquinimod and BG-12, and the monoclonal antibodies rituximab and alemtuzumab in RRMS.

The advent of the new treatments coincides with the Web 2.0 evolution of the internet technology. Web 2.0 offers patients, doctors, and nurses unforeseen possibilities to fundamentally change, and hopefully improve, the ways in which care is delivered and clinical, patient-centered research is performed. The term Web 2.0 is associated with web applications that facilitate participatory information sharing, inter-operability, user-centered design and collaboration on the World Wide Web [1]. A Web 2.0 site allows users to interact and collaborate with each other, e.g. as creators of user-generated content in a virtual community, in contrast to websites where users are limited to the passive viewing of content that was created for them [2].

Basically, e-health 2.0 can be defined as the merging of the Web 2.0 phenomenon within health care [3]. However, e-health 2.0 goes beyond the social networking technology to include a reformative or even revolutionary change in the fields of health care and clinical research [3]. According to O’Grady the main point of e-health 2.0 is the use of social software and its ability to promote collaboration between patients, their caregivers, and medical professionals [3]. Thus, using the web to exchange information with others substantially relates to learning and education about an illness, what treatment options are
available, how to make decisions, and for support [3]. In a broad sense, it can be conceived that Web 2.0 technologies enable and facilitate social networking, participation, openness, and collaboration, within and between health care consumers, caregivers, patients, health professionals, and biomedical researchers [4].

This chapter highlights actual developments at the crossroads of MS treatment and research and interactive applications of the internet, thereby focusing on online self-assessment, interactive web-based care and interactive phase IV research, and their potential for patient empowerment.

2. Multiple sclerosis

2.1 Disease characteristics

MS is a chronic disease of the central nervous system (CNS) that is pathologically characterized by multiple areas of inflammation, demyelination, axonal loss and gliosis, predominantly but not exclusively in the white matter. Compared to other chronic CNS disorders MS is distinguished by a wide range of symptoms and a highly variable course. Typical clinical features are optic neuritis, paresis, diplopia, paresthesias, incoordination, bladder and bowel disturbances, cognitive dysfunction, anxiety, depression and fatigue [5].

In most patients the onset of disease is between 20 and 40 years of age. In 80% to 85% of the patients the initial phase is characterized by relapses and remissions: RRMS. Relapse/remission episodes are alternated by relatively stable periods of months to years. During a relapse symptoms typically evolve over days to weeks, and after a plateau phase often spontaneously improve, completely or incompletely. The total duration of a relapse/remission episode, from initial symptom to final recovery, varies from less than a week to more than half a year.

To explain the etiology of MS it is thought that myelin-specific auto-reactive lymphocytes are primed in the periphery by unknown factors, after which they migrate to the CNS, leading to inflammatory demyelination and axonal loss [6]. Recent studies have suggested that the innate immune system also plays a role both in the initiation and progression of MS [6]. Inflammation composed of mononuclear cells, breakdown of the blood brain barrier, focal plaques of demyelination and axonal damage characterize the acute MS lesions and underlie relapses [7]. Importantly, the frequency and severity of the immune-mediated changes can be reduced by DMDs.

As the disease duration increases the tendency of relapses to recover diminishes, which results in a higher risk of relapse-related deficits and a step-wise accrual of disability. Eventually, after a period of 10 to 20 years, most RRMS patients transgress to the secondary progressive phase (SPMS), characterized by a relentless continuous progression of disability. In about 15% of the MS patients symptoms start insidiously and continue to slowly progress without relapses, the primary progressive course (PPMS). In both SPMS and PPMS clinical deficits mainly result from axonal degeneration, whereas inflammation plays only a minor role. Accordingly, DMDs are not efficacious in SPMS and PPMS.

2.2 Diagnosis

In the last two decades the sensitivity and specificity of the MS diagnosis has considerably improved due to two developments. Firstly, the wide-spread use of the magnetic resonance imaging (MRI) technique for detection of lesions in brain and spinal cord, and secondly,
new diagnostic criteria proposed by McDonald et al.. The improved diagnosis in combination with the availability of DMDs has increased doctors’ awareness of MS as a possible cause of an episode of CNS disturbances in young adults. In such patients ancillary MRI and cerebrospinal fluid (CSF) analyses may yield abnormal findings that, in combination with the clinical features, justify the diagnosis possible or definite RRMS according to the revised McDonald criteria [8]. Patients who do not fulfill these criteria and in whom other disorders have been adequately excluded are diagnosed as having a so-called clinically isolated syndrome (CIS) suggestive of MS, briefly CIS [8]. A CIS may be monofocal – when clinical abnormalities relate to a single CNS lesion – or multifocal, and often involve the optic nerve, brainstem, cerebellum, spinal cord, or cerebral hemispheres [8].

On T2-weighed brain MRI the great majority of MS patients show multiple hyper-intense lesions. These are typically ovoid shaped with the longitudinal axis perpendicular to the ventricles, of varying hyper-intensity, and located peri-ventricular, juxta-cortical or infratentorial in an asymmetric bilateral pattern [8]. In most MS patients MRI of the spinal cord also shows T2 hyper-intense abnormalities, and the absence of spinal lesions on a technically adequate MRI scan is considered a red flag.

2.3 Assessment and treatment of major symptoms

Fatigue

Fatigue is reported by over 80% of MS patients [9] and often interferes with family life, work or social activities [10]. It is a major determinant of impaired health-related quality of life (HRQoL) in MS [11]. Psychometrically validated questionnaires for measuring MS-related fatigue are the Fatigue Impact Scale (FIS), the Modified Fatigue Impact Scale (MFIS), and the Fatigue Severity Scale (FSS). Treatment options include a management program for a more efficient use of energy, progressive resistance training, cognitive behavioral therapy, and pharmacotherapy. Drugs that are believed to potentially improve MS-related fatigue are amantadine, 4-aminopyridine, 3,4-diaminopyridine, and modafinil. When 6 to 8 weeks after start of a drug treatment the patient has not experienced a relevant decrease in fatigue, the treatment is discontinued and a different drug is considered.

Bladder dysfunction

Symptoms of bladder dysfunction are uncommon at presentation but frequently develop in the course of the disease, and are often associated with spastic paraparesis and sexual problems [5]. The increased urge and voiding frequency result from detrusor muscle over-activity and detrusor-sphincter dyssynergia. Urinary tract infections, resulting from incomplete bladder emptying, are a frequent complication and may lead to worsening of MS symptoms. A 3-day Voiding Diary, the Urinary Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7) are validated tools to comprehensively assess bladder dysfunction in MS. Pharmacotherapeutic options include anticholinergics, cannabinoids and botulinum toxin.

Anxiety and depression

Anxiety and depression are increasingly being recognized as frequent symptoms in MS and as a major determinant of worsened HRQoL [11]. The Hospital Anxiety and Depression Scale (HADS) questionnaire is a validated assessment tool. In daily practice anxiety
disorders, and to a lesser degree depression, are often under-diagnosed in MS patients. As a consequence, patients are deprived of psychological and pharmacological treatments that might be effective in reducing symptoms and disease burden.

Cognitive impairment

cognitive disturbances are a prominent feature of MS, occurring in about half of all patients [12] and in one third of patients with early RRMS [13]. The most frequently impaired domains are complex attention, information processing speed, and memory and executive functions. MS patients with problems in cognitive performance have increased odds of becoming unemployed [12]. Importantly, cognitive symptoms in early RRMS are predictive of disability several years later [14], and in benign RRMS failure on neuropsychological tests predicts clinical worsening over a 3-year period [15]. The detection of cognitive impairment in a RRMS patient is a reason to evaluate the current policy. Routine evaluation of cognition is useful for helping patients to address ensuing problems and to detect cognitive decline as a sign of disease progression or treatment failure [16]. Two neuropsychological test batteries have been developed for use in MS patients, the Brief Repeatable Neuropsychological Battery (BRNB) and the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS) [17]. The high rater and patient burden (the MACFIMS taking around 90 minutes to administer) and the high degree of expertise needed to administer, seriously limit the utility of BRNB and MACFIMS in patient care and clinical trials [17]. A recent study reported the preliminary validation of a brief computerized cognitive battery in RRMS [17]. Previous data supported the reliability of the Symbol Digit Modalities Test (SDMT) and the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) as potential tools for screening and monitoring of cognition in MS [18]. Studies investigating the utility of the SDMT as an online test are ongoing. Neuropsychological (memory) training, aiming to improve or stabilize cognitive performance, and adjustment of coping strategies are management options. Drugs for treatment of cognitive symptoms are under study, although presently no pharmacotherapy is available [17].

2.4 Disease modifying drugs

The DMDs exert their effect by modifying immune mechanisms related to the inflammatory disease process, and thus prevent demyelination and axonal damage. The first-line DMDs INFB and GA combine a moderate efficacy with proven safety, in both the short and the long term. In contrast, the highly efficacious DMDs natalizumab, fingolimod and cladribine are more likely to have potentially serious side effects on the short term, whereas their long term safety still has to be established. The ongoing debate on the optimal use of the DMDs in RRMS patients directly relates to their perceived benefits and risks.

In the escalating treatment approach naïve patients are first prescribed a moderately efficacious DMD, and in case of an insufficient response the drug is discontinued and a more potent DMD is started. This step-wise regimen is deemed appropriate in patients with low disability and a favorable prognosis. The alternative induction regimen is considered in treatment-naïve patients who, in spite of a short disease duration, already have acquired permanent neurological deficits due to frequent or severe relapses, and with a poor prognosis. The aim is to induce a substantial and long-lasting reduction in disease activity, in order that future relapses can be prevented by a moderately efficacious DMD. The inductive effects of the immunosuppressive agents mitoxantrone and cyclophosphamide...
have been studied in clinical trials. Natalizumab is, strictly speaking, not an inductive agent, as its discontinuation is followed by a reappearance of disease activity. In either scenario, escalation or induction, there is a need to closely monitor disease activity, in order to prevent further increase in disability (escalation regimen) or unnecessary risk of serious side effects (induction regimen).

2.5 Concept of (very) early treatment
Pathological findings indicate that inflammation occurring early in the disease leads to axonal damage and permanent tissue loss. These histological changes are in due course mirrored by the appearance of permanent T1-weighed hypo-intense lesions, and brain and spinal cord atrophy on MRI. Recent epidemiological data indicate that as soon as a disability level of Expanded Disability Status Score (EDSS) 3 or 4 has been reached, the increase in disability during the further course of the disease no longer relates to relapses or treatment with DMDs. Interestingly, observational data indicate that start of DMD treatment within 24 months of disease onset, and even more so in the first 12 months, is associated with less long-term disability, later transgression to SPMS and a slower progression during SPMS. The concept of (very) early DMD treatment is based on these and related studies and proposes to start treatment after the first episode, including CIS, or at least in the first 12 to 24 months. However, the disease course and accrual of disability is highly variable between patients. So, in order not to unnecessarily treat patients who would have a benign course without treatment, the (very) early use of DMDs is restricted to those patients in whom prognostic features are unfavorable.

2.6 Prognostic features
There is a body of evidence suggesting that to a certain degree the short-term disease course can be predicted from the presence or absence of specific clinical, MRI and CSF findings. However, the methodological limitations of the investigations on the predictive value of parameters with respect to the long-term disability make that in individual patients a formal prognosis cannot be established. Yet, a comprehensive appraisal of the available patient data might justify an ‘educated guess’ on a patient’s prospects, especially for the short term. The following clinical characteristics of a first RRMS episode or of CIS are considered prognostically unfavorable: multifocal symptoms, pyramidal, cerebellar, or sphincter symptoms, need of steroid treatment, and incomplete recovery. In patients with two or more relapses a short interval between the first and the second attack is unfavorable, as is the occurrence of three or more relapses in the first three years. Some abnormalities suggestive of MS on diagnostic MRI also have a prognostic relevance: the occurrence of three or more T2-weighed hyper-intense lesions, two or more infra-tentorial lesions, corpus callosum lesions, cortical lesions, diffuse lesions in the cerebral spinal cord, cerebral or cervical spinal cord atrophy, T1-weighed hypo-intense lesions, and one or more gadolinium-enhancing lesions. Finally, the presence of immunoglobuline G oligoclonal bands (IgG-OCB), intrathecal immunoglobulin M (IgM) synthesis, and a high concentration of light chain neurofilament on CSF analyses have also been associated with a less favorable course.

2.7 Therapeutic goals
Conventional clinical measures of the effectiveness of DMD treatment include the number and severity of relapses, need of steroid-treatment for relapses, and EDSS or Multiple
Sclerosis Functional Composite (MSFC) score (disability). In clinically stable patients new or enlarged T2-weighed hyper-intense lesions, new or enlarged T1-weighed hypo-intense lesions or gadolinium-enhanced T1-weighted MRI lesions, and (increase of) cerebral or spinal cord atrophy all reflect subclinical disease activity. Clinical and MRI parameters may be combined into a composite measure of disease activity or disease free status. Thus, in a recent study sustained freedom of disease activity was defined as the patient having no relapse, no 3-month sustained increase in EDSS, and no new MRI lesions (no T1 gadolinium-enhancing or new/enlarged T2 lesions) over a specified period [19]. The ultimate goal of DMD treatment is not only to prevent clinical and MRI disease activity, but also the transgression to SPMS. For DMDs to have a maximum chance to obtain this long-term goal, treatment should not only be started timely but also managed in such a way that EDSS 3 to 4 is not reached. To this end the following short-term clinical and MRI measures of disease activity may be monitored: occurrence of a relapse, change in disability (EDSS), new or enlarging T2-weighed hyper-intense or T1-weighed hypo-intense lesions, gadolinium-enhancing lesions, and (increase of) brain and spinal cord atrophy. It was recently found that early EDSS change and medication possession ratio are moderate predictors of long-term disability [20] [21]. A higher medication possession ratio predicted better long-term clinical outcomes, while greater early increase in EDSS score predicted worse outcomes. In contrast, change in MRI parameters were only weakly associated with long-term outcome [20]. So, it seems that short-term clinical changes and adherence to DMD treatment have a higher prognostic value than MRI measures. The added value of composite measures remains to be established.

3. E-health 2.0 in multiple sclerosis treatment

The availability of a broad range of DMDs for the treatment of RRMS, the prognostic relevance of early disease activity in CIS and RRMS, the prognostic relevance of early disease activity after start of treatment, the importance of the timing of treatment initiation, the potentially serious side effects of the newer drugs and our ignorance of their long-term risks, implicate that in the coming years MS treatment is increasingly being characterized by both complexity and personalization. In this context, the use of Web 2.0 techniques for interactive online monitoring and care might make a crucial contribution to the management of MS patients. Interactive online monitoring and care are believed to enhance the chances that the potential benefits of the DMDs are realized and that treatment goals are achieved.

3.1 Monitoring

Aspects of monitoring

Monitoring may be defined as repeated testing aimed at guiding and adjusting the management of a chronic or recurrent condition [22]. Minimum criteria for monitoring are that clinically significant changes in the condition or effect of treatment occur over time, that there is an available monitoring test that reliably detects clinically significant changes when they occur, and that cost-effective action can be taken on the basis of the test result [22]. As monitoring involves a series of tests over time a monitoring strategy needs to consider frequency and timing of tests in the context of a series of sequential results [22]. It should address the following questions: Who should be monitored? What outcome should be monitored? What test should be used? When, and at what interval? Who should do the
monitoring? What action to take on the monitoring result? [23]. Only since the occurrence in 2005 of progressive multifocal leukencephalopathy, a potentially lethal CNS disorder, as a rare side effect of natalizumab has monitoring become a topic in MS neurology. As monitoring of disease activity and adverse events in DMD-treated patients is a rather recent development, most of the fundamental questions regarding the optimal monitoring strategies still have to be answered.

**Monitoring in multiple sclerosis**

In view of the nature of the parameters for current or future disease activity mentioned above, the conventional monitoring of CIS and RRMS patients focuses on doctor-centered clinical and MRI outcomes. In fact, in daily clinical practice the natural course of the disease as well as the course after start of DMD treatment is monitored by means of assessments during the patients’ regular visits to the out-patient department, with intervals that usually vary from 3 to 12 months. Doctors and nurses ask about relevant changes in symptoms, notably those suggestive of a relapse or progression, and ideally disability is measured using a validated clinical scale, e.g. the EDSS or MSFC. However, in general neurological practices the regular and standardized quantification of disability is probably an exception, rather than the rule. Moreover, it is doubtful whether CIS and RRMS patients have a T2-weighted and gadolinium-enhanced T1-weighted brain and spinal MRI scan performed on a sufficiently regular basis, given the costs of scanning time and of gadolinium. Importantly, practical circumstances, like travel distances and expenses, scarcity of qualified medical personnel, and restricted availability of MRI machines, often prevent the conventional monitoring process from being optimal, both in terms of the selection of patients, the tests used, and the frequency of assessments.

**Monitoring by online self-assessment**

Compared to doctor-centered or technical measures patient-reported outcomes have various advantages. Firstly, they have an intrinsic clinical relevance; secondly, data are less expensive to acquire; and thirdly, the assessment schedule is more flexible and can easily be adjusted to changing circumstances or unexpected outcomes. For example, the frequency of assessments can be increased if there is a narrow time window regarding the start of DMD treatment, or if a dose increase is associated with a risk of serious side effects. Traditionally, patient-reported outcomes are obtained via questionnaires on site, per postal questionnaire or per telephone. Prospective well-designed studies in MS patients using patient-reported outcomes via the internet are scarce. Yet, especially the web-based applications of accepted and validated measures have obvious advantages compared to doctor-centered outcomes obtained on site. Online questionnaires and diaries can be completed at home at time points convenient to patients; errors and missing data are minimized by instantaneous checks of completeness and consistency; and electronic data capture into a database prevents transmission errors. Moreover, as online questionnaires are ready available, assessment intervals can be short and flexible, and monitoring schedules can easily be tailored to individual needs, e.g. for detection of early changes. Finally, patient-centered data may provide information that complements or partially substitutes doctor-reported data, rendering monitoring less time-consuming for neurologists and MS nurses.

We investigated in an exploratory manner whether monitoring by online self-assessments with monthly intervals is feasible and informative in RRMS patients starting a DMD [24].
We included 167 RRMS patients in a 12-month observational study during which patients were asked to complete two short questionnaires, on HRQoL and fatigue, at monthly intervals. 73.7% completed both questionnaires at all 13 time points, whereas 85.1% of the patients completed both questionnaires in at least 7 of the 13 time points. For both questionnaires the mean changes between baseline and month 12 were similar to those found in studies using paper questionnaires completed on site or at home with 6-month intervals. These data indicate the feasibility and potential usefulness of monitoring by monthly online self-assessment. Intensive online monitoring appears to be an informative and patient-friendly tool for assessing short-term effectiveness. It can be argued that the full advantages of monitoring by online self-assessment are only realized in the context of an interactive care setting.

3.2 Treatment and care
In the past two decades the expanding knowledge on the inflammatory mechanisms leading to tissue damage in MS and the pathophysiological changes underlying the major symptoms have initiated a plethora of therapeutic studies, varying from placebo-controlled randomized trials to observational studies and anecdotal reports. Study data have given neurologists and MS-nurses ample opportunities to substantially lessen the disease burden in their patients. However, it is recognized that as yet most patients insufficiently benefit from the insights and therapeutic potential generated by research data [25]. The unmet needs in MS patients relate to the fact that the implementation of treatment options is hampered by limited resources and organizational insufficiencies and inefficiencies. One of the measures to improve both effectiveness and efficiency of MS care may be the introduction of Web 2.0 applications in the care process.

Interactive online care
To outline the potential advantages of interactive online care in MS patients a typical example, the MSmonitor project, is described here. This project aims to improve MS care in the Netherlands by interactive use of the internet on the basis of patient-reported outcomes, obtained via online self-assessment. MSmonitor started in 2010 and at present 12 MS centers and neurological practices participate. Basically, every six months patients complete the Multiple Sclerosis Impact Profile (MSIP) and the Multiple Sclerosis Quality of Life-54 (MSQoL-54) or the Leeds Multiple Sclerosis Quality of Life (LMSQoL) scale online 1 to 2 weeks before their regular out-patient visit.

The MSIP is a psychometrically validated outcome measure for disability and disability perception in MS patients [26]. The scale is based on the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO). The MSIP disability data are complementary to the doctor-centered EDSS. In those neurological practices where the EDSS cannot be assessed (time constraints, lack of qualified personnel) the MSIP disability data may provide a validated patient-reported alternative. In addition, the disability perception part of the MSIP informs on the subjective dimension of symptoms and signs and provides a systematic, complete, detailed, and quantitative overview of experienced burden of disease. In the online application of the MSIP answers that represent a worsening compared to the previous assessment are automatically highlighted. Thus, the online MSIP gives a quick screen of both the current condition and of recent changes. The individual data are made available on the secured project website to treating MS-nurse and neurologist, and helps them to prepare the on site consultation. In fact, the MSIP overview...
may guide the conversation between patient and MS-nurse or neurologist, by focusing on changes with high disability perception. The inventory of symptoms according to relevance and the preview opportunity for caregivers are thought to enhance effectiveness and efficiency of outpatient visits.

The MSQoL-54 and the LMSQoL measure HRQoL. HRQoL is a multidimensional concept related to a person’s perception of well-being and the level of role fulfillment across a range of dimensions, including physical, psychosocial, social and symptom-related dimensions [27]. It is a term that refers to an individual’s assessment of how a health problem as well as its treatment affect his/her ability to perform activities and roles that he/she values [28]. A critical element of HRQoL is that it reflects the patient's assessment of the impact of his/her illness, not the physician's perspective, as most physiologically oriented measures and traditional clinical scales do [29]. As HRQoL comprises not only perceptions of physical functioning and general health, but also perceived psychological functioning and social/role functioning [30], its assessment is thought to provide a comprehensive evaluation of an individual’s health [31]. Using the MSIP it was demonstrated that HRQoL impairment in MS patients was most related to emotional problems, cognitive dysfunction, and sleep disturbances [26]. In DMD-treated patients the HRQoL data help to assess the treatment’s overall effectiveness from the patient’s perspective [32] [33].

In addition to the 6-monthly assessments, MS-nurse and neurologist may in selected patients activate these scales at additional time points or activate symptom-related questionnaires for in-depth assessment of specific symptoms, e.g. when a subjective worsening has been reported by e-mail or by phone; or to obtain valid pre-treatment values by repeated measurements; or to closely follow initial changes after start of treatment; or to evaluate specific treatment effects. An example: the beneficial effect of symptomatic drug treatment of MS-related fatigue usually manifests itself within 6 to 8 weeks. The low chance of a relevant change in fatigue and the possibility of side effects urge a timely evaluation. The repeated online use of the MFIS informs on the baseline condition and the degree of short-term change in MS-related fatigue. Other symptoms can also be quantified online by symptom-specific validated questionnaires, such as depression and anxiety by the HADS, bladder symptoms by a Voiding Diary, and comorbidity by the Self-Report Comorbidity Questionnaire for Multiple Sclerosis (SRCQ-MS). The SDMT may be included for assessment of cognition, as soon as preliminary data on the validity of the online version have been confirmed.

The combination of the instantaneous availability of patient-reported outcomes on disability, disability perception and symptoms prior to and during out-patient visits, the possibility of repeated assessments and of symptom-related in–depth measurements, the online evaluation by caregivers via the secured website, and the flexible feedback by short-message service (SMS) or e-mail has the potential to improve effectiveness and efficiency of MS treatment and care. Moreover, an outcome value that represents a clinically minimally important change may be set as an alert level. As soon as the outcome variable reaches the predefined limit an alert pops up on the screen, a message is sent by e-mail to the neurologist or MS-nurse, or appears on their screen after log in, whatever is decided. E.g. patients with a tendency to depressive symptoms who start INFb treatment may use the online HADS for monitoring mood with a predefined alert set-point. Preliminary data from the MSmonitor project indicate that the use of Web 2.0 technology in MS care benefits both patient and caregiver in terms of flexibility and efficiency, as self-assessment, evaluation,
and feedback do not depend on consulting hours or simultaneous availability of patient and caregiver. A next step will be the development of an interactive education program for patients and caregivers.

4. E-health 2.0 in multiple sclerosis research

4.1 Web-based phase IV research
Randomized placebo-controlled phase II/III trials provide data on a DMD’s efficacy to reduce in the short term the frequency and severity of the clinical manifestations of inflammation (relapses) and of surrogate parameters (MRI lesions). Such trials do not inform on the long-term efficacy, in terms of preventing disability increase or conversion to SPMS, or slowing progression during SPMS; nor on long-term side effects. It is also of note that in fact the phase II/III results do not pertain to patients treated in real life, as data are typically obtained from selected patients, treated in dedicated MS centers in large, often academic hospitals.

Data on the long-term effectiveness and safety in patients treated in daily practice can be acquired in observational phase IV studies, and the internet enables virtually every MS patient to participate in such studies. Within the framework of a prospective observational study every patient who starts a treatment can be asked to regularly complete online a set of standard questions concerning aspects of effectiveness and side effects. In a web-based study a patient’s participation does not depend on his/her geographic location or distance to out-patient clinic, and therefore an online study may include large cohorts in whole regions or even countries. Methodologically, the representative character of the online acquired data enables the external validation of the phase III data. As to drug safety, an online observational study covering a whole population or region with virtually no restrictive selection criteria yields an almost complete picture of adverse events in real life.

4.2 Interactive observational research
An important aspect of web-based phase IV research is that study data on effectiveness and safety from individual patients can be made available to treating MS-nurse or neurologist for monitoring purposes. We started in the Netherlands the Dutch MS Study, a prospective, online, patient-centred study of long-term disability, disability perception and HRQoL in patients with MS or CIS. Every 6 months patients complete the MSIP (disability and disability perception) and the MSQoL-54 (HRQoL). Disease characteristics and demographic and medication data are recorded online at the start of a patient’s participation, and thereafter relapses and medication use can be updated every month. A patient may consent to give his/her MS-nurse or neurologist access to the study data for evaluation of treatment or the natural course of the disease. Actually, as the information provided by the study data may lead to an adjustment of the disease management, e.g. discontinuation or change of medication, we have created a setting in which there is an interaction between observation and daily practice. As a result, the study data may give insight not only into factors that relate to changes in the disease course, but also in those that drive the decisions regarding treatment and care processes.

The study’s inclusion criteria are: having the diagnosis MS or CIS, and being willing and able to participate in the investigations. The latter criterion implies the availability of a
4.3 Adherence and adherence research

The effectiveness of DMD treatment depends on adequate adherence and implies year-long continued drug administration with a minimum of missed doses. The two aspects of inadequate adherence are: 1) missing doses, and 2) early discontinuation for other reason than insufficient response, serious side effects or persistent moderate side effects. Patients treated with the injectable first-line DMDs miss 30% of the doses [34], and the 6-month discontinuation rate may be as high as 27% [35]. It has been known that DMD discontinuation for more than three months is associated with a increased risk of relapses. Recent data show that in RRMS patients the degree of disability eight years after start of INFb-1a treatment is related to the medication possession ratio [21] Adherence is influenced by the socio-economic situation, health care and caregivers, disease, treatment and patient characteristics. In MS patients self-efficacy expectations are thought to be related to adherence, as are patient education and optimal support. A detailed knowledge of those aspects of care that significantly relate to adherence may lead to adherence-improving measures. Moreover, the identification of patients at high risk of inadequate adherence could lead to more efficient care.

The CAIR (Correlative analyses of Adherence In Relapsing remitting multiple sclerosis) study investigates in GA-treated RRMS patients the relationship between drug adherence and multidisciplinary care, as well as factors associated with adherence [36]. The study is a prospective, web-based, patient-centered, nation-wide, observational cohort study in the Netherlands. The primary objective is to investigate whether adherence is associated with specific disciplines of care or quantities of specific care. The secondary objective is to investigate whether adherence is associated with specific aspects of the socio-economic situation, health care and caregivers, disease, treatment or patient characteristics.

All data are acquired online via a study website (www.cairstudie.nl) and all RRMS patients in the Netherlands starting GA treatment were eligible. At pre-defined and random time-points patients are requested to complete a short questionnaire on missed doses and eventual discontinuation. Every two weeks patients record the care they received (discipline, frequency, duration). The Dutch Adherence Questionnaire-90 (DAQ-90), a 90-item questionnaire based on the World Health Organization (WHO) 2003 report on adherence, comprehensively assesses the five domains of evidence-based determinants of adherence: socio-economic, health care and caregivers, disease, treatment, and patient-related factors. Self-efficacy is assessed by the Multiple Sclerosis Self-Efficacy Scale (MSSES), and mood and HRQoL by the MSQoL-54.

Importantly, adherence data from online self-assessment can be used in an interactive web-based care setting, like the MSmonitor project. Access to individual data enables neurologist and MS-nurse to monitor adherence, whereas the regular completion of a short questionnaire may per se be an adherence promoting activity. Based on the online data caregivers will be able to give feedback to patients with inadequate adherence, whereas the choice of adherence improving measures can be guided by the pre-treatment online inventory of risk factors (DAQ-90). It is expected that in the near future online monitoring of adherence and interactive web-based care, tailored to the individual risk factors, may help to improve adherence and thus the effectiveness of DMD treatments.
4.4 Patient empowerment
The interactive use of the internet for monitoring and care purposes enables patients to better understand and evaluate their own conditions. As a result, patients become educated partners in the relation with caregivers and may take initiatives as to how their MS should be managed. Interactive programs that inform and educate on treatment options, e.g. using evidence-based algorithms, will help patients to position themselves as independent actors in the process of benefit-to-risk evaluation and shared decision making. As the Web 2.0 technology is likely to increase knowledge and awareness in many individual patients, it may thus collectively transform web-based patient communities into grassroots movements that initiate and drive research projects on topics that are relevant to patients but do not appeal to pharmaceutical companies and academia.

5. Conclusion
Current developments suggest that in the coming years Web 2.0 technologies will be integrated in the treatment and care of MS patients and in MS research. Monitoring of effectiveness, safety and adherence by online self-assessment is the basis of interactive online care and (interactive) observational phase IV research. E-health 2.0 developments are likely to increase patients’ empowerment and will favor patient-driven decision making and research. In the context of ever diminishing health care resources and an increasing likelihood of drastic changes in the health care system, for MS patients e-health 2.0 could make the difference between, on the one hand, an ongoing suboptimal use of ever more efficacious drugs with persistence of unmet needs, and, on the other hand, personalized, more effective and safe treatments that may prevent long-term disability.

6. References


A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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