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Approved drugs and their problems in patient care: Routes of administration and dosing

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Abstract

Problems in patient care with regard to route of administration and dosing of currently approved drugs are reviewed. Dose, frequency and route of administration can make a difference in efficacy, side effects, quality of life, antigenicity, cost, and compliance.

Keywords: Multiple sclerosis; Treatment; Routes; Dosing; Problems

1. Introduction

Prior to 1993 there were no U.S. or European federally approved drugs for use in patients with multiple sclerosis (MS). Instead a potpourri of therapies was tried empirically based on theoretical considerations, results from controversial or less rigorous studies, and extrapolation from therapies found to be effective in other autoimmune disorders including an animal model of MS, experimental allergic encephalomyelitis. Since that time progress has been steady and impressive if not spectacular. There are now 6 FDA approved drugs available for treating clinically isolated syndromes suggestive of MS, relapsing remitting MS (RRMS), other relapsing forms of MS, secondary progressive MS, and progressive relapsing MS (Table 1). These drugs, although not curative, have all been shown to be effective therapies. Unfortunately, it is estimated that of the estimated 2.2 million individuals with MS worldwide, only about 6 hundred thousand now take disease modifying drugs regularly. Avonex, Betaseron, Copaxone, and Rebif have been found to have excellent risk-benefit profiles, whereas Tysabri and Novantrone while also effective therapies have potentially more serious effects [1–8]. Indeed, Tysabri was voluntarily withdrawn from the market, because progressive multifocal leukoencephalopathy occurred in 3 patients of whom 2 died [2]. After a thorough study of patients who received Tysabri, this drug was recently approved for release by the FDA.

This paper deals with problems of the approved drugs in patient care as related to routes of administration and dosing. Side effects and toxicity of these drugs will be discussed by others.

2. Problems with route of administration

In Table 1, route, dose, and frequency of administration of approved drugs, is summarized. Four of the 6 approved drugs are proteins — 3 recombinant interferons (Betaseron, Rebif, Avonex) and Tysabri, a humanized monoclonal antibody and α-4 integrin antagonist, one a random polymer of 4 basic amino acids L-glutamine, lysine, alanine, and tyrosine (Copaxone), and the last, Novantrone, a small molecular weight immunosuppressive agent used to treat various malignant disorders [1,3–8].

Problems with the use of these approved drugs are shown in Table 2 and include: adverse effects of varying severity; a palliative rather than curative effect on disease course [1,3–6]; high cost, uneven availability worldwide, and sometimes suboptimal patient compliance [9]; the lack of an effective oral therapy at present [10,11]; the absence of an inexpensive, reliable, readily available biomarker of disease activity for titrating drug dose; limited information on optimal drug dose, frequency of administration, or duration of long term effectiveness [1,3–6]; the variable appearance of neutralizing

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Table 1
Approved MS therapies

Drug	Dose	Route	Frequency
Avonex (IFNβ-1α)	30 μg	I.M.	Weekly
Betaseron (IFNβ-1b)	0.25 mg	S.C.	EOD
Rebif (IFNβ-1α)	22/44 μg	S.C.	TIW
Copaxone (Glatiramer Acetate)	20 mg	S.C.	Daily
Novantrone (Mitoxantrone)	12 mg/m^2	I.V.	Q3M
Tysabri (Natalizumab)	300 mg	I.V.	Q4W

antibodies (NAb's) which may interfere with drug effectiveness (interferons and Tysabri) [7,12] and the need for more direct drug efficacy comparisons [13,14].

With regard to route of administration (Table 3), all subcutaneous or IV administered approved drugs can be associated with local injection site reactions typically mild in nature but occasionally more problematic. Skin reactions have been described in 85–92% of patients on Betaseron or Rebif and include local inflammation, pain, edema, plaques, granulomas and induration [15–18]. While most such reactions are not severe, skin necrosis and ulceration can occur in about 5% of patients. It is hypothesized that poor injection technique, wider width and shorter needle length, angular injection into dermis or epidermis, choice of site, repeated injections at the same site, inadequate training, improper skin cleaning, excessive exposure to sunlight, and acidic pH may all play a role in causing local skin reactions [15–18]. Cutaneous reactions are also common with subcutaneous Copaxone injections and include erythema (66%), hemorrhage (5%), induration (13%), inflammation (49%), mass (27%), pain (73%), pruritus (40%), urticaria (5%) and welts (11%) [15]. Lipoatrophy has also been noted in some patients. In an attempt to reduce injection site reactions, patients taking interferon subcutaneously are advised to rotate injection sites, inject medication at room temperature, use auto injectors, take analgesics, and apply topical ice or steroid ointments as needed [15–18]. It is controversial whether slower titration of beta interferons reduces the incidence of skin reactions [19]. Fortunately, the incidence of adverse skin reactions appears to decrease over time. Nevertheless, in one study 22% of all interferon dropouts due to adverse reactions were attributed to local skin reactions [20].

Table 2
Problems with approved drugs

- Cost, availability, compliance
- Palliative not curative
- Optimal dose, frequency, duration of effect unclear
- No effective oral therapy
- Risk–benefit ratio varies
- Need more direct drug comparisons
- NAb's — effect efficacy (IFNβ, Tysabri)
- Definition of treatment failure, how treated?
- Need better lab markers for efficacy/dose

Table 3
Problems with route of administration

- Site reactions
- Systemic reactions
- Antigenicity
  Route effect (?)
  IFNβ Rebif ≃ Betaseron > Avonex
  Tysabri — 6% persistent NAb's
- Cost — drug, needles, syringes, training, nurses
- Compliance

Cutaneous reactions are much less commonly seen with intramuscular interferon beta injections although injection site pain may be seen in about 8% of patients and infection site inflammation in 6% [15]. Rarely infections including localized intramuscular abscess can develop. However, in a direct comparison study between Rebif and Avonex intramuscular skin reactions of various types were more common than expected occurring in 28% of the latter [14]. In addition to adverse reactions, administration of intramuscular injections may be more difficult for some patients particularly those with disabling neurologic deficits or cognitive problems sometimes requiring another individual to administer medication. Although rare, minor local reactions following intravenous administration of Novantrone or Tysabri have been described usually due to inadvertent extravasation of injected material. Extravasation of Novantrone at the infusion site can lead to local erythema, blue skin discoloration, swelling, pain, phlebitis and even skin necrosis [15]. Interestingly, infusion related reactions with Tysabri are more likely to occur in the 6% of patients who are persistently NAb positive [21].

Organ specific and systemic reactions can occur with all MS approved medications and reflect inherent characteristics of the drug, dose, route and frequency of administration, as well as host factors.

NAb's develop to the beta interferons and Tysabri which if persistent and of high titer can interfere with clinical (relapses, progression) and MRI efficacy. The frequency and

Table 4
Problems with dose/frequency

- Optimal dose/frequency of IFNβ unknown
  Higher dose/frequent IFNβ more effective than lower dose/frequent
  High dose/frequent IFNβ more effective than high dose/infrequent
  Single weekly high dose IFNβ-1α = double dose once weekly IFNβ-1α
  AE's may increase with higher dose
  Antigenicity may change with dose/frequency
- Copaxone — only 20 mg/day dose tested
- Tysabri — monthly 3 mg/Kg dose = 6 mg/Kg
  300 mg/month (AFFIRM, SENTINEL)
- Mitoxantrone — 12 mg/m^2 may be more effective than 5 mg/m^2
  Other doses/frequency proposed
  AE's effect duration/dose
- Need biomarkers/individualize dose (?)
- Pediatric therapy — dose (?), frequency/dose (?)
- Compliance with high frequency/dose