A Practical Guide to Disease Modifying Therapies

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Disclosures

- Consulting and speaking for Sanofi Genzyme
- Speaking for Teva Neuroscience
Learning Objectives

- Identify known and novel benefits associated with the use of MS therapies, and the strategies used to maximize patient outcomes
- Identify risks associated with the use of MS therapies, and the mitigating strategies used to minimize those risks
Outline

- Evolving concepts in choosing a DMT
- Overview of currently approved disease modifying therapies (DMTs)
- Review post-marketing comparative studies
- Overview of risk mitigation strategies
- Conclusions
Evolving Concepts

In Choosing a Disease Modifying Therapy
MS Treatment Landscape: New agents

- The MS treatment landscape has changed considerably over the last 10 years.
- Evidence from trials and observation studies has shown that not all patients have similar responses to the same agent.
- More opportunities for personalized or individualized treatment:
  - Disease type, presence of activity
  - Disease aggressiveness (highly active disease)
  - Timing of treatment
  - Escalation versus induction therapy
  - Treatment goals
  - Risks

Comi et al. 2017, Damico 2017
The new MS course definitions allow for classification into relapsing-remitting MS, secondary progressive and primary progressive MS.

Further, progressive MS can be classified as with/without activity and/or progression.

Highlighting disease “activity” and the “relapsing” component has allowed for a more tailored, but also wider treatment landscape.

Source: Lublin et al., 2014.

Source: Lublin et al., 2014.
Identifying patients with highly active MS

▪ There is no consensus on highly active MS.

▪ Highly active MS may portend worse outcomes.

▪ What is highly active MS:
  ▪ Frequent relapses (two relapses in one year).
  ▪ Incomplete recovery.
  ▪ Severe relapses
  ▪ Multifocal presentation
  ▪ MRI activity (high lesion burden, frequent contrast enhancing lesions)

Comi et al 2017
Early Treatment

- With few exceptions, treatment should be offered early
- Emerging evidence continues to support the role of early treatment in patients with relapsing forms of MS.

Figure from Comi et al Lancet 2017
Treatment Strategies: Escalation or Induction

- Based on each individual patient’s risk (prognostic profile)
- Escalation: Start treatment with a safe agent and move to more aggressive treatment if disease breakthrough occurs
- Induction: Start treatment with a strong, highly efficacious, agent especially in patients with high risk for disability
  - By definition: Induction therapies should have a long-lasting effect
  - Only alemtuzumab and mitoxantrone can be considered induction therapies
  - Ocreluzimab

Comi et al 2017, Damico 2017
Escalation does not work for everyone

- Traditional treatment approaches in one study resulted in poor medium term performance with discontinuation due to breakthrough and side effects

Granqvist et al. JAMA Neuro 2018
Therapeutic goals

▪ Reduction/halting in rate of relapses
▪ Reduction/halting in MRI activity
▪ Reduction/halting in disability progression
▪ NEDA = No evidence of disease activity (clinical, MRI and disability progression), also known as NEDA-3
▪ NEDA-4 includes no brain atrophy (or more broadly, no degeneration).
Risks – discussed in detail later

- Each agent or class of agents has a different risk profile
- The risk benefit profile for a specific agent is not constant during the disease course.
  - Benefits are greater earlier in the disease course because of greater likelihood for inflammation
  - Risks may increase with age because of the higher frequency of other co-morbidities
- It is important to choose a therapy with an acceptable risk profile for the patient
- Risk assessment algorithms for each agent and each patient group need to be developed.
  - Based on the risk/benefit profile of the therapy and the specific patient population.
Overview of current DMTs
## Summary of Pivotal Clinical Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy (% reduction in relapse rate)</th>
<th>Common side effects</th>
<th>Serious adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-interferons</td>
<td>32% to 35% versus placebo</td>
<td>ISR, flu-like symptoms, ↑ LFTs</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>29% to 34% versus placebo</td>
<td>ISR, lipoatrophy, system reaction</td>
<td></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>68%</td>
<td>Infusion reactions, infections</td>
<td>PML</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>54%, 48% (52% v beta-interferon 1a)</td>
<td>Bradycardia, macular edema, infections</td>
<td>VZV, herpes and other rare infections</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>36%, 31%</td>
<td>GI symptoms, hair thinning, ↑ LFTs</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>49%, 44%</td>
<td>GI symptoms, flushing</td>
<td>Rare PML</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>55%, 49% versus beta-interferon 1b</td>
<td>Infusion reactions, infections</td>
<td>Secondary autoimmunity (thyroid disorders, ITP)</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>46%, 47% versus beta-interferon 1b</td>
<td>Infusion reactions, infections</td>
<td>Rare risk of infection and cancer</td>
</tr>
</tbody>
</table>

ISR = Injection site reaction. LFTs = Liver function tests. PML = Progressive multifocal leuкоencephalopathy. VZV = Varicella Zoster virus. GI = Gastrointestinal, ITP = immune thrombocytopenia purpura

Table adapted from Dr. Anne Cross. Also see Comi et al, Lancet 2017
Comparative Studies
Comparative Effectiveness

Assumptions
Knowledge from clinical trials

- Several head-to-head trials have shown a relatively similar efficacy for interferon-beta and glatiramer acetate.

- Fingolimod resulted in a 52% reduction in relapse rates compared to interferon beta-1a IM weekly.

- Teriflunomide seems to have a similar efficacy to interferon beta-1a

- Alemtuzumab resulted in a 49%-55% reduction in relapses rates compared to interferon beta-1a SC three times weekly.

- Ocrelizumab resulted in a 46%-47% reduction in relapses rates compared to interferon beta-1a SC three times weekly.
Comparative Effectiveness

Ocreluzimab  Alemtuzumab  Fingolimod  Glatiramer acetate  Beta interferons

Efficacy

TRANSFORMS
CARE MS I
CARE MS II
Mikol 2008
Lublin 2013
OPERA I
OPERA II
Comparative post-marketing studies

- Only a few, mostly newer, randomized clinical trials used an active comparator.
- Trials are not strictly comparable.
- Post-marketing studies rely on statistical modeling (like propensity scores) to make comparisons across treatment groups.
  - Often, but not always, using large cohorts like patient registries.
- Comparative studies help confirm or refute inherent assumptions neurologists make about DMTs.
Fingolimod and injectable therapies

- In the MSBase cohorts, patients switching to injectable therapies or fingolimod were compared.
- Propensity score matching and pairwise censoring were used to control for biases.

The fingolimod group had lower mean relapse rate (0.31 versus .42, p=0.009) and lower hazard to first on-treatment relapse (p=0.04).

- Fingolimod-treated patients were less likely to discontinue treatment (p=0.04)

<table>
<thead>
<tr>
<th>Baseline therapy, No. (%)</th>
<th>Interferon beta-1a, 30 μg IM</th>
<th>Interferon beta-1b, 250 μg SC</th>
<th>Interferon beta-1a, 22μg/44 μg SC</th>
<th>Glatiramer acetate, 20 mg SC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>319 (56.7)</td>
<td>70 (12.5)</td>
<td>106 (18.9)</td>
<td>67 (11.9)</td>
</tr>
<tr>
<td></td>
<td>40 (17.6)</td>
<td>51 (22.4)</td>
<td>85 (37.2)</td>
<td>52 (23.8)</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>90 (23.7)</td>
<td>80 (21.1)</td>
<td>137 (36.9)</td>
<td>72 (19.0)</td>
</tr>
<tr>
<td></td>
<td>32 (21.6)</td>
<td>32 (21.6)</td>
<td>55 (37.2)</td>
<td>29 (19.6)</td>
</tr>
<tr>
<td></td>
<td>.51</td>
<td>.88</td>
<td>.84</td>
<td>.90</td>
</tr>
</tbody>
</table>

He et al. JAMA Neurol 2015
Oral DMTs and injectable therapies

- Retrospective single-center cohort.
- Cox proportional hazards models were used to control for baseline difference.
- Sensitivity analyses using propensity scores.
- Oral and injectable DMTs in this cohort had equal breakthrough disease activity except for Teriflunomide which appeared somewhat less effective than injectable therapies.
Comparative Effectiveness

TRANSFORMS
- CARE MS I
- CARE MS II
- Mikol 2008
- Lublin 2013
- OPERA I
- OPERA II
- He 2015
- Longbrake 2015
Fingolimod, dimethyl fumarate and teriflunomide

- Binomial regression models were used to adjust for difference across pivotal trials for the oral agents.

- This modeling approach showed that fingolimod treatment resulted in higher probability of NEDA compared to the other two agents.

Nixon et al. Adv Ther 2014
Fingolimod and dimethyl fumarate

- Fox et al compared individual data from the dimethyl fumarate pivotal trials and aggregate data from the fingolimod pivotal trials (data were pooled and compared using the matching-adjusted in-direct method).
  - The efficacy of fingolimod and dimethyl fumarate were similar.
  - Patient reported outcomes favored dimethyl fumarate.

- Patients from seven MS clinics in Italy.
  - Patients were either treatment naïve or switching from injectable agents.
  - No significant difference between fingolimod and dimethyl fumarate on NEDA-3 status.
  - No difference on relapse rate
  - Subgroup analysis showed superiority for fingolimod in patients switching from an injectable therapy (HR 0.57, p=0.007).

Fox et al. Current Medical Research and Opinion 2016. Prosperini et al 2018
Comparative Effectiveness

TRANSFORMS
CARE MS I
CARE MS II
Mikol 2008
Lublin 2013
OPERA I
OPERA II
He 2015
Longbrake 2015
Nixon 2014
Fox 2016
Prosperini 2018
Natalizumab & INF-B

- A retrospective study with a small sample size (42 patients in each group).
- Natalizumab was more effective than INF-B 1a SC three times weekly.
  - Relapse rate reduced from 1.5 to 0.24 for natalizumab and 1.1 to 0.55 for INF-B (p=0.0125 for the comparison, adjusted for baseline differences).
Natalizumab & fingolimod

- Using MSBase, Kalincik et al evaluated patients with breakthrough disease activity on injectable therapies.
  - The relapse rate decreased from 1.5 to 0.2 for natalizumab and 0.4 for fingolimod (a 50% relative difference, p=0.002).
  - Natalizumab had a near 3 fold higher rate of disability improvement (regression), P<0.001.
  - No difference in the rate of disability progression.
  - The effect on relapse rates was sustained over 2 years.

Kalincik et al Ann Neurol 2015
Natalizumab & fingolimod

- In patients who did not respond to injectable therapies:
  - Natalizumab resulted in higher percentages of relapse-free patients (80% vs. 66% for fingolimod, p=0.015).
  - Natalizumab had a higher percentage of patients with NEDA-3 (70% vs. 40%, p<0.001)
  - Natalizumab also had higher percentage of disability improvement patients and lower MRI activity.
  - No difference in disability progression

- Swiss registry.
  - Agents used as second-line treatment.
  - Natalizumab-treated patients were less likely to experience a relapse.
  - And more likely to experience disability improvement.

Baroncini et al. MSJ 2016. Lorscheider et al. MSJ 2018
Alemtuzumab, natalizumab, fingolimod & INF-B

- Using the MSBase observational cohort and 6 non-MSBase centers.
- Alemtuzumab and natalizumab have similar effects on relapses rates.
- Alemtuzumab is superior to fingolimod and INF-B in its effect on relapses rates.
- All agents were comparable in their effect on disability accumulation.
- Natalizumab superior to alemtuzumab in enabling recovery from disability.
Rituximab

- In a retrospective study of prospectively collected data, investigators compared Rituximab to other commonly prescribed DMTs.

- Patients treated with rituximab had lower rates of disease activity compared to injectable therapies and dimethyl fumarate.

- Disease activity rates were also lower, compared to fingolimod and natalizumab, but did not reach statistical significance.

- Rituximab was associated with better adherence.

Granqvist et al. JAMA Neuro 2018
Rituximab and natalizumab

- Observational study on the effectiveness of rituximab.
- A group of rituximab-treated patients were matched to natalizumab-treated patients.
- No significant difference was found on their effect on NEDA.
- No relapses occurred in the 16 patients who switched from natalizumab to rituximab.

Scotti et al. PLOS one 2018
Comparative Effectiveness

Efficacy

Beta interferons
Teriflunomide
Glatiramer acetate
Fingolimod
Dimethyl fumarate
Rituximab
Alemtuzumab
Natalizumab
Ocrelizumab

TRANSFORMS CARE MS I
CARE MS II
Lanzillo 2012
Kalincik 2014
Baronchini 2016
Lorscheider 2015
Kalincik 2017
OPERA I
He 2015
OPERA II
Nixon 2014
Fox 2016
Granovski 2018
Prosperini 2018

Lublin 2013
Kalincik 2014
Kalincik 2017
Granqvist 2018
Scotti 2018
Risk Mitigation
# Common Risks associated with DMTs

Table 1. Risks of licensed, frequently used and anticipated multiple sclerosis therapies.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Known risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a, 1b</td>
<td>Injection-site reactions, ‘flu-like’ syndrome, depression, lower birth weight, shorter birth length, preterm birth, liver enzyme elevations, pregnancy category C</td>
<td>Lu et al.⁴</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Injection-site reactions, chest tightness, tachycardia, flushing, dyspnoea, allergic reactions, pregnancy category B</td>
<td>Boster et al.⁵</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Allergic reactions, progressive multifocal leucoencephalopathy, liver enzyme elevations, tuberculosis, melanoma, pregnancy category C</td>
<td>Langer-Gould et al.⁶</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Infections, liver enzyme elevations, hypertension, bradycardia, macular oedema, neoplasia, foetal risk, pregnancy category C</td>
<td>Kappos et al.⁷</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Diarrhoea, nausea, alopecia, elevated alanine aminotransferase, influenza, nausea, paraesthesia, high blood pressure, bone marrow disorder hepatotoxicity, teratogenicity, pregnancy category X</td>
<td>O’Conner et al.⁸</td>
</tr>
<tr>
<td>BG-12</td>
<td>Flushing, gastrointestinal events, decreased lymphocyte count, elevated liver aminotransferase, pregnancy category NA</td>
<td>Gold et al.⁹</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Acute leukaemia, cardiac insufficiency, amenorrhea, infections, pregnancy category D</td>
<td>Stroet et al.¹⁰</td>
</tr>
<tr>
<td>Cyclophosphamide⁵</td>
<td>Nausea/vomiting, alopecia, haemorrhagic cystitis, myelosuppression, infections, infertility, pulmonary fibrosis, secondary cancer, lymphoma, bladder cancer, amenorrhea, pregnancy category D</td>
<td>Jeffery¹¹</td>
</tr>
<tr>
<td>Azathioprine⁵</td>
<td>Secondary cancer</td>
<td>Confavreux et al.¹²</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Infusion reactions, infections, autoimmune (thyroid, ITP, Goodpasture), pregnancy category C</td>
<td>Coles et al.¹³</td>
</tr>
</tbody>
</table>

ITP: idiopathic thrombocytopenic purpura. ⁵Approved drugs for non-multiple sclerosis conditions, with relatively frequent off-label use for multiple sclerosis.
Risk mitigation

- Interferon Beta:
  - Baseline and periodic monitoring of complete blood count (CBC) and liver function testing (LFT)s.
  - Choose different option, if possible, in patients at high risk for liver problems or patients with severe depression.
  - Monitor and treat depressive symptoms. Discontinue if severe.
  - Educate patients about risk of stroke.
Risk mitigation

- Glatiramer acetate:
  - No significant risk mitigation strategies needed.
  - Educate patients about possible post-injection reaction.
Natalizumab and the risk of PML

- Three risk factors for natalizumab-associated PML have been identified and include:
  - Duration of treatment (the risk being greatest after 2 years).
  - Prior treatment with immunosuppressive agents.
  - Exposure to the JCV (as determined by anti-JCV antibody titer).

- The risk for natalizumab-associated PML ranges from <1/1000 in patients who have never been exposed to the virus (irrespective of the other risk factors) to ~10/1000 for patients with all three risk factors.

# Natalizumab and the risk of PML

## Risk of natalizumab-associated PML

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Anti JCV antibody negative</th>
<th>Anti JCV antibody positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-24 months</td>
<td>&lt;1/1000</td>
<td>No prior immunosuppressive use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior immunosuppressive use</td>
</tr>
<tr>
<td>25-48 months</td>
<td></td>
<td>&lt;1/1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/1000</td>
</tr>
<tr>
<td>49-72 months</td>
<td></td>
<td>3/1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13/1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/1000</td>
</tr>
</tbody>
</table>

Natalizumab and the risk of PML

- The overall risk of PML is 1:250 for all natalizumab treated patients.
- Over 685 cases reported worldwide.
- Despite risk mitigation, the incidence of natalizumab-associated PML has not changed.
- Several studies suggest that the risk has been previously underestimated.
- Risk of PML in early treatment may be higher for older (>44 years-old) patients.
- High positive titers (>0.9 index value) or increasing titers, portend increased risk.
Risk mitigation

- Natalizumab:
  - Assess for 3 PML risk factors.
  - Patients who are JCV antibody negative undergo JCV serology testing every 3-6 months.
  - Patients who are JCV antibody positive and who have been on treatment for for 1-2 years should be counseled on the increased risk of PML.
    - Alternative options should be discussed.
    - Patients should be monitored more closely both clinically and with imaging.
  - Patients with all three risk factors are at a very high risk (1 in 44) for PML.
    - Switching therapy may be advisable.
  - A high positive JCV antibody titer (and/or a rising titer over time) likely infers greater PML risk than a low positive titer.

Risk mitigation

▪ Fingolimod:
  ▪ Prior to initiating treatment, patients should undergo:
    ▪ Baseline VZV serology (vaccination should be offered to those without confirmed prior exposure).
    ▪ Ophthalmology evaluation.
    ▪ Cardiac evaluation (EKG or more extensive cardiac evaluation in those with cardiac risk factors).
  ▪ Monitor patients at first dose for 6 hours (more if cardiac risk high).
  ▪ Periodic ophthalmology evaluation for macular edema.
  ▪ Periodic lab workup including CBC and LFT.
    ▪ Consider holding or discontinuation if lymphocyte count is persistently low. Although evidence suggests no increase in infection rate despite low lymphocyte count.
Risk mitigation

- Fingolimod:
  - Counsel patients on risk of infections.
  - Over 13 cases of PML have been reported.
  - Risk is <0.1 in 1000.
  - Older age (>45-50) and longer treatment duration might be a risk factor.
Risk mitigation

- **Teriflunomide:**
  - Baseline and monthly LFTs for the first 6 months, then periodically.
  - Periodic CBC evaluations.
  - Baseline tuberculosis screen.

- **Pregnancy:**
  - Counsel on risk of teratogenicity for all patients.
  - Baseline pregnancy test.
  - Consider reliable contraception.
  - Prompt washout if pregnancy planned or occurs.
Risk mitigation

- Dimethyl fumarate (DMF):
  - Counsel on gastrointestinal side effects (take with food) and flushing (consider aspirin).
  - Baseline and periodic CBC.
    - Consider holding/discontinuation if persistent low lymphocyte count (less than 500) and/or CD4+ or CD8+ count.
  - Counsel patient on risk of PML.
    - Persistent lymphopenia
    - Older patients.
    - Risk is 0.019/1000

Otaneda continuum aan 2013, Chahin J Neurovirol 2014
Risk mitigation

- Alemtuzumab:
  - Prescribing physicians and patients are required to enroll in the Risk Evaluation Mitigation Strategy (REMS) program.
    - Monthly CBC, serum creatinine and urinalysis as well as thyroid function testing every 3 months for 48 months after the last dose.
    - Baseline and periodic dermatology evaluation.
  - Herpes prophylaxis for at least 2 months or until the CD4+ count is greater than 200.
Risk mitigation

- Ocrelizumab:
  - Screen for Hepatitis B and C at baseline.
  - Periodic CBCs.
  - Monitor for infusion-related reactions.
  - Counsel on risk of cancer:
    - Woman should be screen regularly for breast cancer.
    - Yearly dermatological evaluations.
  - Counsel on risk of infections.
Conclusion

Putting it all together
Choosing a DMT

- Consider patient age and co-morbidities
- Consider disease subtype, duration
- Consider disease severity (activity)
- Consider dose, frequency and mode of administration.
- Consider efficacy.
- Consider risks.
- Consider side effects
Treatment Strategies: Escalation or Induction

- Patients with worse prognosis should be considered for induction therapy or highly efficacious treatment options.
- Patients with a more favorable prognosis should be considered for escalation therapy.
- Counsel on specific risks associated with each therapy.
- Monitor patients clinically and with MRI 6-12 after starting or switching therapies.

Comi et al 2017
Choosing a DMT

Initial choice of therapy

Patients with average active MS
- Dimethyl fumarate
- Teriflunomide*
- Interferon beta and glatiramer acetate

Choice
Side-effects
Suboptimal effect

Suboptimal effect

Patients with aggressive MS
- Natalizumab
- JC virus Ab–
- JC virus Ab+ (high)
- JC virus Ab+ (low)
- Fingolimod
- Alemtuzumab
- Daclizumab

Choice
Side-effects
Suboptimal effect

Escalation of therapy

Natalizumab
- JC virus Ab–
- JC virus Ab+ (high)
- JC virus Ab+ (low)
- Fingolimod
- Alemtuzumab

Choice
Side-effects
Suboptimal effect

Suboptimal effect

Mitoxantrone†

Off-label therapies

B-cell depleting drugs
- Rituximab
- Ofatumumab

Choice
Side-effects
Suboptimal effect

Suboptimal effect

Intense immunosuppression with autologous haemopoietic stem-cell transplantation

Figure from Comi et al Lancet 2017
Takeaway from recent guidelines

▪ AAN and ECTRIMS/EAN

▪ Common recommendations:
  ▪ Initiate DMT in clinically isolated syndrome
  ▪ Initiate DMT for RRMS with clinical or radiological disease activity
  ▪ Clinical and radiological monitoring for efficacy
  ▪ Consider switching if inadequate efficacy (relapse, new MRI lesions ± disability progression)
    ▪ Also if side effects affect adherence and/or adverse events due to DMT (AAN)
  ▪ Continue DMT if RRMS patient is stable
Takeaway from recent guidelines

▪ Secondary progressive MS:
  ▪ ECTRIMS/EAN: Initiate beta-interferon, mitoxantrone, clardibine or ocrelizumab
  ▪ AAN: No specific recommendation

▪ Primary progressive MS: Both recommend considering ocrelizumab

▪ Highly active MS:
  ▪ AAN: alemtuzumab, fingolimod, or natalizumab
  ▪ ECTRIMS/EAN: No specific recommendation
Takeaway from recent guidelines

- Guidelines do not address:
  - Personalized treatment
  - Comparative efficacy
  - Choice of therapy for initiating or switching patients

- “Guidelines cannot replace critical thinking”
Thank You