Monoclonals (RmAb) & Immunoglobulins in Rabies Post-exposure Prophylaxis: An update

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Outline

- Rabies prophylaxis
- RIGs
- Rabishield
- Post-marketing experience
- IAP recommendations
- WHO recommendations
- Conclusions

WHO recommendation

- Post-exposure prophylaxis (PEP) is nearly 100% protective
- Wound care ± RIG + Rabies vaccine

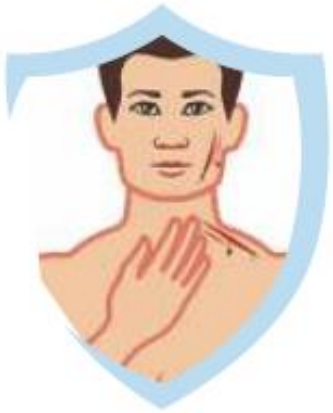
Category	Management
I	No prophylaxis is required
II	Immediate vaccination
III	**Immediate vaccination and RIG**

In Category III bites, Rabies vaccine alone does not provide complete protection

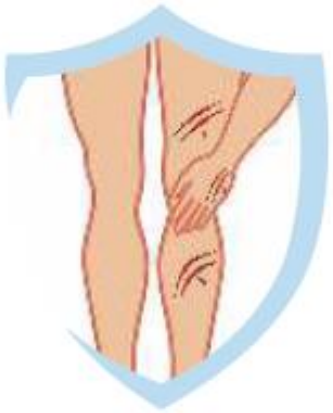
Category III exposures

- Category III exposures include:
  - single or multiple transdermal bites or scratches,
  - contamination of mucous membrane with saliva from licks,
  - licks on broken skin,
  - exposures to bats

Bites where short incubation period is expected



Bites on face, neck region



Multiple site exposures

Bites on fingers and genitalia

Short incubation period is HIGH RISK!!!

Passive prophylaxis

- Rabies vaccines produce antibodies by 7-14 days
- Incubation period can be shorter in case of high risk bites
- Readymade antibodies are a must for immediate protection
- HRIG derived from human volunteers
- ERIG derived from horses

Comparisons between available therapies: Cont.

Specification	HRIG	ERIG	Monoclonal RIG
Clinical Trials	National and International trials are available	Available	Limited trials available
Administration	IM	IM	IM
Recommendations	Recommended by WHO and NCDC	Recommended by WHO and NCDC	-
Adverse reactions	NO	Yes	
Choice of therapy in multiple/severe bites	Preferred	Considered only in the absence of HRIG	Alternative therapy of HRIG

Dosage:

- Human Rabies Immunoglobulin 20 IU per kg of body weight.

- Maximum dosage for HRIG 1500 IU.

Advantages of HRIG:

- Lesser dose require 20IU/kg body weight.
- Can be given in pregnancy and lactation.
- can be given to patient having history of Antisera administration (e.g. Anti snake, AGGS, etc.)
- No Sensitivity test require.
- *HRIG* is Safe and more efficient *as compare to* ***monoclonal*** as have broad coverage.

Issues with blood-derived RIG

- Availability (limited supply, HRIG imported)
- Affordability (expensive, often paid out of pocket)
- Safety (ERIG: risk of anaphylaxis; varying purity; risk of blood borne pathogens)
- Skin test required as per product insert (ERIG)

RIGs availability

- HRIG/ERIG available mostly in urban areas
- But most of the rabies exposures in rural parts
- Access to RIGs is negligible
- Huge disparity of affordability

Therefore RIGs are not available where they are needed the most.

- To overcome these limitations, recombinant monoclonal antibody - Rabishield was standardized by MassBiologics, USA
- Rabishield neutralizes all known isolates of globally prevalent rabies viruses
- Strains from Asia – India, Nepal, Sri Lanka, Thailand, Americas, Africa – neutralized in in-vitro studies
- A phase I study found that Rabishield is safe [Gogtay NJ et al, 2012]
- A Phase 2/3 study in Category 3 patients, Rabishield PEP regimen showed superior immune response vs. HRIG containing regimen at day 14.[Gogtay NJ et al, 2018]

Rabishield publications

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 2800–2810
Vaccine
www.elsevier.com/locate/vaccine

Identification and characterization of a human monoclonal antibody that potently neutralizes a broad panel of rabies virus isolates☆

Susan E. Sloan[a], Cathleen Hanlon[b], William Weldon[b], Michael Niezgoda[b], Jesse Blanton[b], Josh Self[b], Kirk J. Rowley[a], Robert B. Mandell[a,1], Gregory J. Babcock[a], William D. Thomas Jr.[a], Charles E. Rupprecht[b], Donna M. Ambrosino[a,*]

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Abstract

Rabies is a zoonosis that results in millions of human exposures worldwide each year. Human monoclonal antibodies (HuMAbs) that neutralize rabies virus may represent one viable strategy for post-exposure prophylaxis in humans, and have many advantages over current human or equine rabies immune globulin. Transgenic mice carrying human immunoglobulin genes were used to isolate human monoclonal antibodies that neutralized rabies virus. Several HuMAbs were identified that neutralized rabies virus variants from a broad panel of isolates of public health significance. HuMAb 17C7 was the most promising antibody identified because it neutralized all rabies virus isolates tested. HuMAb 17C7 recognizes a conformational epitope on the rabies virus glycoprotein which includes antigenic site III. HuMAb 17C7 protected hamsters from a lethal dose of rabies virus in a well-established in vivo model of post-exposure prophylaxis.

Antiviral Research 91 (2011) 187–194

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

G glycoprotein amino acid residues required for human monoclonal antibody RAB1 neutralization are conserved in rabies virus street isolates

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ABSTRACT

Replacement of polyclonal anti-rabies immunoglobulin (RIG) used in rabies post-exposure prophylaxis (PEP) with a monoclonal antibody will eliminate cost and availability constraints that currently exist using RIG in the developing world. The human monoclonal antibody RAB1 has been shown to neutralize all rabies street isolates tested; however for the laboratory-adapted fixed strain, CVS-11, mutation in the G glycoprotein of amino acid 336 from asparagine (N) to aspartic acid (D) resulted in resistance to neutralization. Interestingly, this same mutation in the G glycoprotein of a second laboratory-adapted fixed strain (ERA) did not confer resistance to RAB1 neutralization. Using cell surface staining and lentivirus pseudotyped with rabies virus G glycoprotein (RABVpp), we identified an amino acid alteration in CVS-11 (K346), not present in ERA (R346), which was required in combination with D336 to confer resistance to RAB1. A complete analysis of G glycoprotein sequences from GenBank demonstrated that no identified rabies isolates contain the necessary combination of G glycoprotein mutations for resistance to RAB1 neutralization, consistent with the broad neutralization of RAB1 observed in direct viral neutralization experiments with street isolates. All combinations of amino acids 336 and 346 reported in the sequence database were engineered into the ERA G glycoprotein and RAB1 was able to neutralize RABVpp bearing ERA G glycoprotein containing all known combinations at these critical residues. These data demonstrate that RAB1 has the capacity to neutralize all identified rabies isolates and a minimum of two distinct mutations in the G glycoprotein are required for abrogation of RAB1 neutralization.

Vaccine 30 (2012) 7315–7320

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and pharmacokinetics of a human monoclonal antibody to rabies virus: A randomized, dose-escalation phase 1 study in adults☆

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Rabies monoclonal antibody
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ABSTRACT

Background: Rabies is an essentially fatal disease that is preventable with the timely administration of post-exposure prophylaxis (PEP). The high cost of PEP, which includes vaccine and hyperimmune globulin, is an impediment to the goal of preventing rabies in the developing world. Recently a recombinant human IgG_1 anti-rabies monoclonal antibody (SII RMab) has been developed in India to replace serum-derived rabies immunoglobulin. The present study was conducted to demonstrate the safety of SII RMab and to determine the dose resulting in neutralizing serum antibody titers comparable to human rabies immunoglobulin (HRIG) when administered in conjunction with rabies vaccine in a simulated PEP regimen.

Methods: This randomized, open label, dose-escalation phase 1 study was conducted in healthy adults at a large tertiary care, referral, public hospital in India. Safety was assessed by active surveillance for adverse events along with standard laboratory evaluations and measurement of anti-drug antibodies (ADA). Anti-rabies antibody levels were measured by rapid fluorescent focus inhibition test (RFFIT) and ELISA. The study duration was 365 days.

Findings: SII RMab was well tolerated with similar frequency of local injection site reactions to HRIG. The geometric mean concentrations of rabies neutralizing antibody in the vaccine plus SII RMab 10 IU/kg cohort were comparable to the vaccine plus HRIG 20 IU/kg cohort throughout the 365-day study period; day 14 geometric mean concentrations 23.4 IU/ml (95% CI 14.3, 38.2) vs. 15.3 IU/ml (95% CI 7.72, 30.3; p = NS), respectively. Future post-exposure prophylaxis studies of SII RMab at a dose of 10 IU/kg in conjunction with vaccine are planned.

Clinical Infectious Diseases

MAJOR ARTICLE

Comparison of a Novel Human Rabies Monoclonal Antibody to Human Rabies Immunoglobulin for Postexposure Prophylaxis: A Phase 2/3, Randomized, Single-Blind, Noninferiority, Controlled Study

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Background. Lack of access to rabies immunoglobulin (RIG) contributes to high rabies mortality. A recombinant human monoclonal antibody (SII RMAb) was tested in a postexposure prophylaxis (PEP) regimen in comparison with a human RIG (HRIG)–containing PEP regimen.

Methods. This was a phase 2/3, randomized, single-blind, noninferiority study conducted in 200 participants with World Health Organization category III suspected rabies exposures. Participants received either SII RMAb or HRIG (1:1 ratio) in wounds and, if required, intramuscularly on day 0, along with 5 doses of rabies vaccine intramuscualarly on days 0, 3, 7, 14 and 28. The primary endpoint was the ratio of the day 14 geometric mean concentration (GMC) of rabies virus neutralizing activity (RVNA) as measured by rapid fluorescent focus inhibition test for SII RMAb recipients relative to HRIG recipients.

Results. One hundred ninety-nine participants received SII RMAb (n = 101) or HRIG (n = 98) and at least 1 dose of vaccine. The day 14 GMC ratio of RVNA for the SII RMAb group relative to the HRIG group was 4.23 (96.9018% confidence interval [CI], 2.59–6.94) with a GMC of of 24.90 IU/mL (95% CI, 18.94–32.74) for SII RMAb recipients and 5.88 IU/mL (95% CI, 4.11–8.41) for HRIG recipients. The majority of local injection site and systemic adverse reactions reported from both groups were mild to moderate in severity.

Conclusions. A PEP regimen containing SII RMAb was safe and demonstrated noninferiority to HRIG PEP in RVNA production. The novel monoclonal potentially offers a safe and potent alternative for the passive component of PEP and could significantly improve the management of bites from suspected rabid animals.

Clincical Trials Registration. CTRI/2012/05/002709.

Dosage & Administration

- PEP - one dose of Rabishield and a full course of rabies vaccination
- **Dose - 3.33 IU/kg body weight**, preferably at the time of the first vaccine dose
- It may also be given through the 7th day after the first dose of vaccine is given

Dosage & Administration

- **Dose of 3.33 IU/kg body-weight offers advantages**
  - More potent than HRIG (20 IU/Kg) and ERIG (40 IU/kg)
  - Significantly **lowers** infiltration volume
  - Greatly **eases** infiltration process
  - More Patient and Doctor convenience
  - Better patient acceptability
- Significantly reduces cost compared to HRIG

How to calculate Dose?

What will be the dose required for Child of 30 Kg body weight?

a) **Dose required for 30 Kg** = **Body weight x 3.33 IU**

30 kg x 3.33 IU = **99.9 or 100 IU**

b) **Dose in ml** = **Dose required for 30 Kg/ Potency**

99.9 IU / 40 IU per ml = **2.5 ml**

Lower volume requirement makes infiltration easier

- Rabishield *vs* ERIG & HRIG: 2.5 ml *vs* 4 ml

Post-marketing experience

- There is an extensive **post-marketing experience** on the product
- Subsequent to its licensure approximately 150,000 vials of Rabishield™ (100 IU/2.5 mL) have been distributed in the market
- **No safety concerns were seen with such wide use of Rabishield**

Global Distribution

Rabishield distributed in 15 countries so far:

- Afghanistan
- Azerbaijan
- Chad
- Dem. Rep. Congo
- Djibouti
- Jordan
- Kyrgyzstan
- Latvia
- Malaysia
- Namibia
- Nepal
- Saudi Arabia
- South Sudan
- Tajikistan
- Uzbekistan

New studies on Rabishield

- A large Phase 4 trial in 4000 patients with category 3 potential rabies exposure is planned across multiple study sites in India
- Regulatory approval has been obtained for this study
- Study will be initiated in mid July 2019

An independent study on Rabishield

- A comparative study between the new RMAb and the RIGs conducted at ARC of KIMS, Bangalore from January to June, 2018
- 397 subjects of 1 to 85 years with category III exposure
  - 142 in RMAb group,
  - 243 in ERIG group &
  - 12 in HRIG group

ORIGINAL ARTICLE

Safety of new indigenous human Rabies Monoclonal Antibody (RMAb) for Post Exposure Prophylaxis

Anwith Huluvadi Shivalingaiah[1], Ravish Haradanhalli Shankaraiah[2], Ashwath Narayana Doddabele Hanumanthaiah[3]

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Abstract

Background: WHO recommended development of Rabies Monoclonal Antibodies (RMAb) to overcome the problems associated with rabies immunoglobulin for post exposure prophylaxis against rabies in all category III exposures. A new indigenous RMAb has been manufactured and marketed in India. The present study was conducted to monitor the post marketing clinical use of RMAb for post exposure prophylaxis. **Aims & Objectives**: To assess the safety of human rabies monoclonal antibodies for post exposure prophylaxis. **Material & Methods**: A comparative study between the new RMAb and the previously established rabies immunoglobulins was conducted at anti-rabies clinic in a Medical college Hospital, Bangalore from January to June, 2018. All the animal bite victims with category III exposure were included in the study. The details regarding their socio demographic profile, characteristics of exposure, post exposure prophylaxis provided and any adverse drug reactions following administration of RMAb were recorded. **Results:** The study included 397 subjects with category III exposure; 142 in RMAb group, 243 in equine rabies immunoglobulin group & 12 in human rabies immunoglobulin group. Majority of the study subjects were males & aged between 1 – 85 years. All the subjects were provided post exposure prophylaxis as recommended by WHO. There were no immediate adverse drug reactions; however, 8% of the subjects had delayed ADRs such as pain at the site of infiltration (4.2%), swelling (2.1%) and wound infection (0.7%); which resolved without any complications. **Conclusion:** The new indigenous human RMAb is safe for post exposure prophylaxis against rabies.

IAP Recommendation

RECOMMENDATIONS

Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) Recommended Immunization Schedule (2018-19) and Update on Immunization for Children Aged 0 Through 18 Years

S BALASUBRAMANIAN, ABHAY SHAH, HARISH K PEMDE, PALLAB CHATTERJEE, S SHIVANANDA, VIJAY KUMAR GUDURU, SANTOSH SOANS, DIGANT SHASTRI AND REMESH KUMAR

From Advisory Committee on Vaccines and Immunization Practices (ACVIP), Indian Academy of Pediatrics, India. Correspondence to: Dr Harish K Pemde, Director Professor, Department of Pediatrics, Lady Hardinge Medical College, Kalawati Saran Childern's Hospital, New Delhi, India. harishpemde@gmail.com

Rabies Human Monoclonal Antibody (RHMAB) – IAP recommendation

This newly introduced monoclonal antibody has emerged as a safe and potent alternative to rabies immunoglobulin. The WHO position paper on Rabies in 2018 has also suggested encouragement of use of this product, if available, instead of RIG. The comparative advantages include easy availability, standardized production quality, possibly greater effectiveness, no requirement of animals in its production, and less adverse events.

In view of the irregular availability and high cost of Rabies immunoglobin (RIG), ACVIP endorses the use of RHMAB as an alternative to RIG – human or equine – along with rabies vaccines in all category-III bites. RHMAB is licensed in India (as Rabisheild, Serum Institute of India; 40 IU/mL) since 2017. The recommended dose is 3.33 IU/kg body weight, preferably at the time of the first vaccine dose. However, this may also be administered up to the 7th day after the first dose of vaccine is given. If the calculated dose is insufficient (to infiltrate all the wounds), it should be diluted in sterile normal saline to get a volume that is enough to be infiltrated around all the wounds.

Rabies Human Monoclonal Antibody (RHMAB) – IAP recommendation

- This newly introduced mAb has emerged as a safe and potent alternative to RIG.
- The comparative advantages over RIGs include
  - Easy availability,
  - Standardized production quality
  - Possibly greater effectiveness
  - No requirement of animals in its production, and
  - Less adverse events

Endorsement by the IAP

- IAP has endorsed Rabishield –
- *'In view of the irregular availability and high cost of RIGs,* ***ACVIP endorses the use of RHMAB as an alternative to RIG – human or equine – along with rabies vaccines in all category-III bites. RHMAB is licensed in India (as Rabishield, Serum Institute of India; 40 IU/mL) since 2017****. The recommended dose is 3.33 IU/kg body weight, preferably at the time of the first vaccine dose'*

WHO Position on RmAb

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

20 APRIL 2018, 93th YEAR / 20 AVRIL 2018, 93e ANNÉE
No 16, 2018, 93, 201–220
http://www.who.int/wer

Contents

Rabies vaccines: WHO position paper – April 2018

Vaccins antirabiques: Note de synthèse de l'OMS – avril 2018

For optimal effectiveness, the maximum dose calculation for RIG is 40 IU/kg body weight for equine derived RIG (eRIG), and 20 IU/kg body weight for human derived RIG (hRIG). Skin testing before eRIG administration should not be done because of its unreliable prediction of adverse effects. However, the treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of RIG administration. If available, the use of mAb products instead of RIG is encouraged. Suturing of wounds should be delayed after RIG infiltration, or if unavoidable, sutures should be loose to allow optimal RIG diffusion.

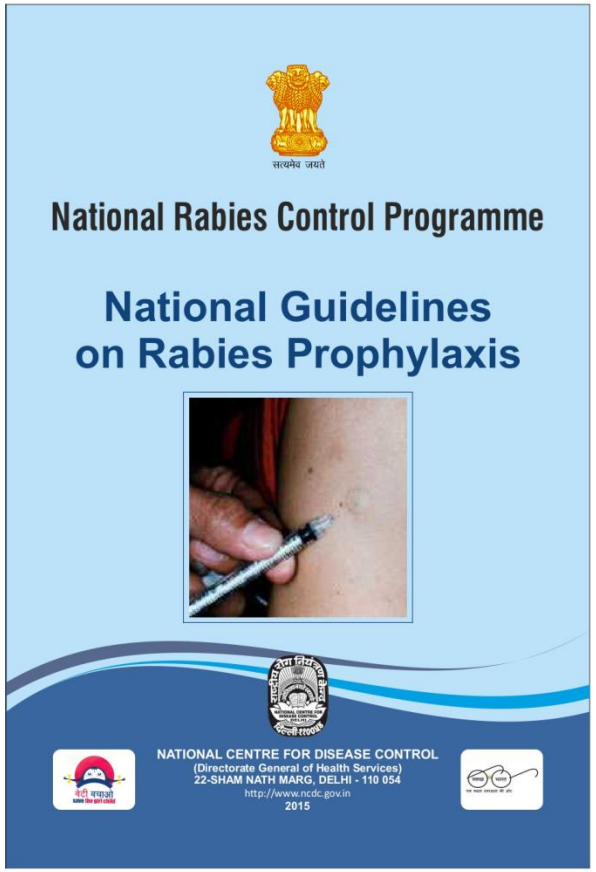
A single monoclonal antibody (mAb) product against rabies, which was licensed in India in 2017, has been demonstrated to be safe and effective in clinical trials. This mAb neutralizes a broad panel of globally prevalent RABV isolates. The comparative advantages of mAb products include large-scale production with standardized quality, greater effectiveness than RIG, elimination of the use of animals in the production process, and reduction in the risk of adverse events.

WHO Expert Consultation on Rabies

Third report

PEP (*28*). Several human mAbs have been tested against rabies. The first (a single mAb) was recently licensed by the Serum Institute of India (*29*). Studies so far show the equivalence of its performance to human RIG. The availability of this mAb could fill critical public health gaps. As it is made by recombinant technology, it will be less prone to problems such as availability, safety and purity. It should be recommended for use in public health programmes, depending on the epidemiological and geographical setting, with monitoring of its safety and efficacy (clinical outcomes) during post-marketing use.

“ Indication: Human Rabies immunoglobulin (HRIG): HRIG are homologous origin and are relatively free from the side effect encountered in a serum of heterologous origin…….” National Guidelines of Rabies Prophylaxis- NCDC-2015.



immunity in the form of ready-made anti-rabies antibodies, before it is physiologically possible for the victim to begin producing his/her own antibodies following anti-rabies vaccination. Anti-rabies serum or RIG has the property of binding with the rabies virus, thereby resulting in neutralization and thus loss of infectivity of the virus and hence it is most logical to infiltrate RIG locally at the site of exposure. Two types of RIGs are available:

Equine Rabies Immunoglobulin (ERIG): ERIG is of heterologous origin produced by hyper-immunisation of horses. Currently manufactured ERIGs are highly purified Fab 2' fragments and the occurrence of adverse events has been significantly reduced. These are produced in the country in public and private sectors. (Annexure 1: Table 1: Currently available ERIG currently manufactured in India)

Since, ERIG are of heterologous origin, they carry a small risk of anaphylactic reaction (1/150,000). However, literature supports that there is no scientific ground for performing a skin test prior to administering ERIG because testing does not predict reactions, and ERIG should be given irrespective of the result of the test. The treating physician should be prepared to manage anaphylaxis, which, although rare, could occur during any stage of administration, even when the skin test did not show any reaction (WHO TRS 2013, pg 43). However, some manufacturers of ERIG still recommend performing a skin test.

Human Rabies Immunoglobulin (HRIG): HRIG are of homologous origin and are relatively free from the side effects encountered in a serum of heterologous origin. However, it is expensive and is imported from other countries. (Annexure 1: Table 2: Currently available HRIG in India). Because of their longer half-life, they are given at half the dose of equine anti-rabies serum.

Indication: RIG should be administered to all category III exposures. However, in immune compromised individuals, RIG should be administered in both category II and III exposures.

Dose of rabies immunoglobulin: The dose of ERIG is 40 IU per kg body weight of patient. The ERIG produced in India contains 300 IU per ml. The dose of the HRIG is 20 IU per kg body weight. HRIG preparation is available in concentration of 150 IU per ml.

Administration of rabies immunoglobulin: The RIG should be brought to room temperature (25°C to 30°C) before administration to the patient.
As much of the calculated dose of RIG as is anatomically feasible should be infiltrated into and around the wound/s. Multiple needle injections into the wound(s) should be avoided. After all the wound(s) has been infiltrated, if any

- ***As per WHO Expert Consultation*** **on Rabies Third Report HRIG must be used for Grade-III exposed patient.**

World Health Organization

TO SUMMARIZE
Advantages of Rabishield

- Recombinant DNA technology
- Adequate supply (easier to produce, mass production, QC easier)
- Reduces risks of adverse reactions
- More potent, less volume required
- No risk of blood borne pathogens
- No skin test required

Summary continued….

- Rabishield is a superior, safer and affordable alternative to blood-derived RIGs which can be made readily available in volumes that will easily match the countrywide demands.
- With this thousands of deaths can be averted.
- Rabishield has been recommended for use in Rabies PEP by WHO and IAP

Thanks